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PERFORMING KIDNEY TRANSPLANTATION IN PEOPLE LIVING WITH ACQUIRED HUMAN IMMUNODEFICIENCY SYNDROME

*¹Maurício Caxias de Souza, ²Valesca Paes de Albuquerque Vieira, ³Antonio Romario Mendes da Silva, ⁴Ciro Gadelha Queiroga, ³Ana Claudia Araújo da Silva, ³Edina Silva Costa, ⁴Tandara Maria Ponte Costa, ⁴David Silveira Marinho, ⁴Daniel Costa Cavalcante Aragão, ⁴Sara Rocha Barreira, ⁴Dionísia Ericy Menezes Teixeira, ⁴Glauber Gean de Vasconcelos, ⁴Germana Medeiros Mendes Damasceno, ⁴José Carlos Rodrigues Nascimento, ⁴André Freire Fuentes, ⁴Rômulo da Costa Farias, ⁴Laio Ladislau Lopes Lima, ⁴Larissa Garcia Gondim, ⁵Aline de Albuquerque Oliveira, ⁴Francisco Andrade Dias Júnior, ⁴Rafael Costa Lima Maia, ⁴Inara Nobre de Castro and ⁴Jennifer de Melo Rocha

¹Enfermeiro. Membro do Grupo de Estudos e Pesquisas em Saúde Coletiva (GEPSC/CNPq) da Universidade Federal de Mato Grosso do Sul (UFMS) (BR); ²Enfermeira de Centro Cirúrgico e Transplantes de Órgãos, Ceará (BR); ³Pesquisadores Independentes de Enfermagem e Ciências da Saúde no Brasil (BR); ⁴Médicos Pesquisadores Independentes, Especialidades de Cardiologia, Anestesiologia, Cirurgia Geral, Transplante de Órgãos, Urologia e Neurocirurgia (BR); ⁵Estudante da Graduação em Medicina da Faculdade Christus, (BR)

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*Corresponding author: Maurício Caxias de Souza

ABSTRACT

The objective was to present the main considerations about kidney transplantation in people living with HIV. In the last decade, with the advent of Highly Active Antiretroviral Therapy (ART), the evolution of people infected with the Acquired Human Immunodeficiency Virus has changed significantly, with a marked decrease in morbidity and mortality rates in this population. In this sense, the number of HIV-positive people with chronic kidney disease in need of dialysis therapy is progressively increasing. In view of the above, kidney transplantation, which was previously considered an absolute contraindication for such patients, has now been considered an alternative for renal function replacement therapy. Questions about the use of immunosuppressants in this group of patients and their possible action by increasing HIV replication, given the risk of opportunistic infections and the development of neoplasms, are widely discussed. However, clinical experience in this area shows that the use of these drugs for seropositive people seems to be safe, including reports of antiretroviral action of some of the immunosuppressive drugs. There are currently few reports of transplants in this population. In summary, data from the relevant scientific literature suggest that kidney transplantation, following patient selection criteria, appears to be a safe alternative as renal replacement therapy in HIV-positive patients.

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INTRODUCTION

In the last decade, with the advent of Highly Active Antiretroviral Therapy (ART), the evolution of people infected with the Acquired Human Immunodeficiency Virus has changed significantly, with a marked decrease in morbidity and mortality rates in this population [1]. In this new scenario, chronic diseases become part of the natural history of HIV infection, and thus, the definition of therapeutic

approaches for these cases becomes fundamentally relevant. In clinical practice, the prevalence of chronic kidney disease in HIV-infected patients has been increasing progressively [2, 3]. Chronic kidney disease can develop as a complication of the evolution and treatment of HIV-seropositive patients, as well as it can affect these patients independently, similarly to what happens in the general population [3]. Currently, chronic kidney disease has a significant impact on the clinical course of HIV-positive patients. HIV-related nephropathy is now the third leading cause of stage V chronic kidney

disease among African Americans in the United States [4, 5]. The introduction of the ART regimen also increased the survival of HIV-positive patients on dialysis. In Brazil, there are currently about 500 HIV positive patients receiving renal replacement therapy, according to data from the Brazilian Society of Nephrology [6, 7]. Faced with this new reality, kidney transplantation, which used to be an absolute contraindication for such patients, is now considered an alternative therapy to replace renal function [7]. In this article, the main considerations about kidney transplantation in people living with HIV will be presented. Justified by its extreme relevance to the academic, scientific and methodological community that permeates the medical and health sciences.

Guiding question or defined as a research problem: What materials are available in the scientific literature about kidney transplants in people living with HIV?

METHOD

This is a quantitative study, of a qualitative and systematic-organized nature, of the integrative review type of current literature. This method aims to group and synthesize research results on a given topic, in an organized way so that it contributes to a deepening of knowledge about the issue addressed [8]. This method has been used in the production of articles, dissertations and theses in the health area in recent decades. A qualitative, systematic and integrative study of the literature was carried out on the scientific productions based on research on kidney transplantation in patients with hiv, in the national and international context, in the health area [9]. This method allows "[...] the search, critical evaluation and synthesis of available evidence on the investigated topic". For the elaboration of this study proposal, six steps will be used, in order to organize the information collected and systematize it [10].

1st stage: elaboration of the guiding question. 2nd stage: search or sampling in the literature. 3rd stage: data collection. At this stage, what will be extracted from the selected studies will be defined, in order to organize the key information in a concise manner for the construction of the study. 4th stage: critical analysis of the included studies. Always taking into account the guiding question as the basis for any analysis. 5th stage: discussion of the results. In this phase, the results obtained in the research will be discussed and a critical analysis will be carried out about what was evidenced. 6th stage: presentation of the integrative review. This is the phase where the study will be properly prepared [11, 12]. The articles will be selected from the Virtual Health Library (VHL) database: LILACS (Latin American and Caribbean Literature in Health Sciences) and MEDLINE (Medical Literature Analysis and Retrievel System Online). The descriptors used will be: Kidney Transplantation; HIV; Journal Article; Research Support as Topic, through the Boolean operator "AND", in order to facilitate searches for materials indexed in the databases". The research universe consisted of online articles in the field of health, related to the proposed theme, through access to the VHL database. The sample will be determined considering the following inclusion criteria: being available in the selected databases, contemplating the proposed theme, being available in full text, being article-type publications, in the period from 2010 to 2022. The exclusion criteria were: dissertations and theses, be in Spanish only, as well as unavailable complete texts and do not contemplate the proposed theme.

RESULTS AND DISCUSSION

Renal transplantation versus people living with HIV: In view of the significant increase in the survival rate of HIV-positive patients after the advent of the ART era, kidney transplantation has come to be considered an alternative treatment for chronic kidney disease in this population. However, many questions have been raised about safety and ethics related to organ transplantation in HIV-positive patients [13].

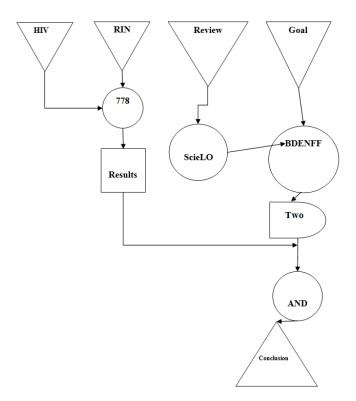


Figure: Research Flowchart

Ouestions about the use of living donors and about criteria for allocating deceased donors to these patients continue to be topics of discussion. Allocation of organs from HIV-positive deceased donors to HIV-positive patients was used in some studies, but cases of superinfection were described and this practice was abandoned [14]. Kidney transplantation in HIV positive patients can be performed with living donors. However, it is recommended that donors be informed that organ transplantation in HIV-infected patients is a recent therapeutic alternative in clinical practice. Another worrying aspect in the context of transplants in this group of patients is the need to use immunosuppressants and their possible action by increasing HIV replication, in addition to the risk of opportunistic infections and the development of neoplasms. However, clinical experience in this area shows that the use of these drugs for seropositive patients appears to be safe [15]. The main aspects related to kidney transplantation in this population will be presented below. Kidney transplantation - pre-ART era Before the emergence of the ART era, publications on kidney transplantation in HIV-positive patients were limited to isolated case reports or small numbers of patients. One of the first publications was made in the early 1990s by the University of Minnesota, which analyzed 11 HIV-positive patients undergoing kidney transplantation [16]. The results showed a mortality rate of 36%. One patient died from sepsis two months after transplantation, and three patients developed AIDS and died within 13 months. Graft survival after 30 months was 54%. In order to study the impact of immunosuppression on kidney transplantation in HIV-infected patients, for example, we will cite the time of progression to AIDS in three groups of HIV-positive patients: kidney transplant patients (n=25), hemophiliacs (n= 42) and infected patients after blood transfusion (n=28). There was a trend towards earlier development of AIDS (15 months) in transplant patients (16%) than in the other groups. However, from the 15th month onwards, the tendency to develop AIDS is equal in the three groups, reaching statistical significance from the fifth year of follow-up [17].

The largest analysis of kidney transplants in HIV-positive patients in the pre-ART period was based on data from the USRDS (United States Renal Data System), analyzing kidney transplants performed between 1987 and 1997. The results showed worse patient survival in the fifth year post-transplant (71% vs. 78% in the control group) and of the renal graft (44% vs. 61% in the control group). In the multivariate analysis, HIV infection was related as an independent

factor of mortality for recipients of deceased donors and also of graft loss [18]. These results supported the restriction of the indication of kidney transplantation for HIV-positive patients. Kidney transplantation - post-ART era In the late 1990s, with the advent of the ART era, there was a significant improvement in HIV-related morbidity and mortality. This improvement was also reflected in the mortality rates of HIV-positive patients on dialysis, which decreased significantly, equaling the mortality rate of HIV-seronegative patients on a dialysis program. Survival of HIV-positive dialysis patients has increased from 56% (before 1990) to 74% (late 1990s) [19]. These results have led to a reassessment of kidney transplantation as a treatment option for HIV-positive patients with advanced-stage chronic kidney disease. One of the first publications was by Stock et al., from the University of California. For HIV positive patients to become eligible for kidney transplantation, the following criteria were considered: undetectable viral load (RNA negative for HIV in plasma) for three months, CD4+ T cell count > 200 cells/mm3 for six months, and absence of of opportunistic infection or carcinoma. Ten patients undergoing kidney transplantation were included [20].

At 36 months of follow-up, all were alive, with a functioning graft. The renal graft rejection rate was 50%. All patients were maintained on an ART regimen. Viral load remained undetectable in all patients, and the number of CD4 cells remained stable. These results were encouraging to indicate kidney transplantation as a treatment option for HIV-positive patients with well-controlled disease. Several other reports have been published reinforcing this treatment alternative [21]. In 2003, 26 seropositive patients who received kidney transplantation. Patient (92%) and graft (85%) survival rates at 10 months were comparable to those of HIV-negative patients. The rejection rate in HIV-infected patients was 37%14. Analysis of data from the USRDS registry of deceased donor kidney transplantation from 1996 to 2001 showed that, of 27,851 patients with available HIV serology, only 47 patients (0.2%) were HIV positive. Of these, 12.8% were black. The survival of HIV positive patients after three years was 95%. Only two HIV-positive patients died (4.3%), compared with 12.8% in the HIV-negative group [22]. These good results may have been influenced by the stricter criteria by transplant centers in the selection of HIV-positive recipients for kidney transplantation. Another possible bias in this analysis may have been the greater use of induction therapy in the immunosuppression of seropositive recipients. Based on these results, the authors proposed kidney transplantation for HIV-positive patients as a more viable treatment strategy after the advent of the ART [23]. In a prospective study, 40 HIV-positive kidney transplant recipients were studied. Inclusion criteria were similar to those described by Stock et al. (HIV negative, RNA < 400 copies/mL and absolute number of CD4+ cells > 200 cells/mm3). The results showed that patient survival in the first and second year post-transplant was 85% and 82%, respectively, similar to results obtained in other groups of high-risk patients and higher than HIV-positive patients on dialysis [23].

We analyzed kidneys from the same deceased donor transplanted in patients with and without HIV, data obtained from the United Network for Organ Sharing (UNOS) in the period from 1997 to 2004. In this analysis, 38 HIV positive patients and 38 HIV negative patients who received kidneys from the same donors. Although not statistically significant, patient and graft survival in the HIV-positive group was superior when compared to the HIV-negative group [24]. More recently, 39,501 kidney transplant patients from the UNOS registry were analyzed from 2004 to 2006, which showed that, although patient survival was similar in HIV-positive and HIVnegative patients, graft survival was significantly lower in HIV cases. positive (87.9% vs. 94.6% in HIV positive). A group from the University of Detroit evaluated the influence of HIV-positive recipient characteristics on kidney transplantation and published an analysis of the evolution of eight seropositive kidney transplant patients with other factors of worse prognosis, such as virus C coinfection and immunological sensitization in a mean time of 15 months [25]. The survival rates found were 100% for the patient and 88% for the graft at the end of the evaluated period. In this study, only one of the patients developed acute rejection (13%). On the other

hand, high rates of acute rejection in HIV-positive transplant recipients were described in a study that evaluated 18 patients undergoing kidney transplantation. The authors described a 52% incidence of acute rejection in the first year of follow-up and 73% in three years, in agreement with the results previously shown by the Stock group in 2003 [26]. In Brazil, there are still no specific records on the activity of transplantation in HIV-positive patients. We recently performed a kidney transplant in a 61-year-old patient with chronic kidney disease secondary to polycystic kidney disease, infected with HIV seven years before transplantation. At the time of diagnosis of HIV infection, the patient received antiretroviral treatment consisting of zidovudine (AZT,® AstraZeneca) 600 mg/day, 3Tc (lamivudine; Epivir®, GlaxoSmith) 75 mg/day and atazanavir (Revataz®, Bristol-Myers Squibb) 400 mg/day. He evolved with a good response, and six months after the start of treatment he had an undetectable viral load, which remained that way throughout the course [27]. The CD4+ lymphocyte count also always remained above 500 cells/mm3. The patient developed stage V chronic kidney disease, undergoing hemodialysis for five and a half years. At the time of transplantation, he had a negative plasma HIV-RNA and a CD4+ lymphocyte count of 464 cells/mm3. Kidney transplantation, performed with a living donor, was uneventful and the patient had an immediate drop in serum creatinine. The immunosuppression regimen included induction with Basiliximab (Simulect®, Novartis) and maintenance with cyclosporine (Sandimmun®, Novartis), sirolimus (Rapamune®, Wyeth) and prednisone. Despite having been prescribed only half of the usual doses of the drugs cyclosporine and sirolimus, the patient evolved with extremely high blood levels [28]. The concentration analyzed six days after the use of cyclosporine was 1,131 ng/mL and that of sirolimus was 56.1 ng/mL, being readjusted to 25% of the usual dose. Currently, two years after kidney transplantation, the patient is doing well, with good renal graft function, with an undetectable viral load and a CD4+ lymphocyte count of 645 cells/mm3. Thus, considering the benefits of the ART era, kidney transplantation in HIV-infected patients has come to be considered an alternative treatment that tends to present itself more frequently in clinical practice [29]. Faced with this new reality, the need arose to establish criteria for the practice of organ transplants in this population. Recently, based on the studies with the greatest impact on kidney transplantation in HIV-infected patients, the main recommendations were gathered to consider the patient a candidate for recipient [30].

Kidney transplantation; Immunosuppression and HIV/AIDS

The use of immunosuppressive drugs in organ transplantation in HIVinfected patients has generally been shown to be effective and safe, since some of these drugs also have antiretroviral action. However, due to the drug interaction between some ART therapy drugs and immunosuppressants, monitoring of blood levels immunosuppressants should be performed more frequently, with dosage adjustments whenever necessary [31]. For many years, HIV infection was considered a contraindication to organ transplantation, based on the principle that, in the presence of immunosuppression, there would be an environment that would favor viral replication. However, more recently, studies have shown that some of the immunosuppressive drugs used in transplantation, such as calcineurin inhibitors (cyclosporine and tacrolimus), sirolimus and mycophenolic acid, have antiretroviral action [32]. Cyclosporine is a calcineurin inhibitor that has properties capable of inhibiting HIV replication. This effect is the result of cyclosporine binding to cyclophilin A, preventing cyclophilin from forming the p55Gag/cyclophilin protein complex, necessary for HIV maturation and replication. It is known that HIV is only able to replicate on activated CD4 T cells. Considering that cyclosporine inhibits T cell activation, via IL-2 inhibition, it decreases the number of activated CD4 T cells, thus decreasing the pool of CD4+ T cells available for viral replication [33]. Cyclosporine also appears to have an anti-apoptotic effect on CD4+ T lymphocytes. In this sense, cyclosporine A prevented apoptosis of T lymphocytes in peripheral blood samples from HIVpositive individuals in vitro. Few studies have shown the action of tacrolimus as an antiretroviral. The action of tacrolimus inhibiting viral proliferation in chronically HIV-infected cells. Sirolimus, an mTOR (mamalian target ofrapamycin) inhibitor, is an immunosuppressant with immunomodulatory activity [34]. The drug is able to decrease the expression of the viral coreceptor CCR5 in T lymphocytes and monocytes at the transcriptional level. The CCR5 receptor is essential for the transmission and replication of HIV, which is evidenced by the fact that individuals who do not express this protein are proven resistant to HIV infection. The use of azathioprine has been associated with an increase in viral replication, while the opposite seems to happen with the use of mycophenolate mofetil. Mycophenolate mofetil (MMF), a prodrug of mycophenolic acid, is another immunosuppressant with a demonstrated antiretroviral effect [35].

The drug appears to have synergistic activity on the action of nucleoside analogue reverse transcriptase inhibitors, one of the classic components used in the regimen to treat HIV infection. This synergism is due to the depletion of an intracellular enzyme called deoxyguanosine triphosphate, essential for HIV replication. Prednisolone increases the population of CD4+ T lymphocytes [35]. Another study showed that prednisolone works by suppressing HIV viral load and inhibiting CCL2, a pro-inflammatory cytokine induced by HIV infection. Regarding the use of anti-CD3 antibodies, monoclonal or polyclonal, it is worth noting that their use is not recommended in HIV positive patients. It is a potent immunosuppressive drug capable of inducing depletion of CD4+ T lymphocytes, thus increasing the risk of disease progression in addition to the risk of developing opportunistic infections [36]. Drug interactions between immunosuppressants and ART The concomitant use of immunosuppressive and antiretroviral drugs is necessary in the context of organ transplants in HIV-positive recipients. Complex pharmacokinetic and pharmacodynamic interactions between these drugs are described in the literature, thus there is a need for strict monitoring of therapeutic levels both to keep HIV positive infection under control and to avoid rejection and toxicity by immunosuppressants [37]. The most classic pharmacokinetic interactions are between protease inhibitors commonly used for the treatment of HIV-positive patients and calcineurin inhibitors (cyclosporine and tacrolimus) or mTOR inhibitors (sirolimus and everolimus). This interaction is due to the fact that both the protease inhibitors and the immunosuppressants described above are metabolized via the cytochrome P450 pathway, which contributes to the increase in blood levels of immunosuppressants. Based on this, it is suggested in the literature that HIV-positive patients should start using calcineurin inhibitors four weeks before transplantation (in the case of transplantation with a living donor), with monitoring of therapeutic drug levels for pre-transplantation adjustment [38]. Such conduct aims to enable the transplant to be performed in the presence of therapeutic levels of immunosuppressants, minimizing the risk of toxicity or, less frequently, of underexposure to the drug. In view of the pharmacological interactions that lead to increased blood levels of calcineurin inhibitors and mTOR inhibitors, we must emphasize the high risk of toxicity to the aforementioned drugs, including the possibility of developing thrombotic microangiopathy [39].

Thrombotic microangiopathy is the histological manifestation of hemolytic uremic syndrome and occurs as a post-transplantation complication in an incidence ranging from 0.8% to 14% of kidney transplants. To this we must add the fact that HIV infection is a proven risk factor for the development of thrombotic microangiopathy. Recently, cases of hemolytic-uremic syndrome associated with sirolimus use have been described, 32 possibly resulting from sirolimus-induced reduction in VEGF expression (which is an important factor in maintaining vascular endothelium viability) [39]. Furthermore, there is evidence that the association of sirolimus at high blood levels with cyclosporine also contributes to the pathogenesis of this entity. Mycophenolate sodium and mycophenolate mofetil are considered safe alternatives for immunosuppression in kidney transplantation in HIV-positive patients with few interactions with other drugs commonly used in the ART regimen [40]. However, diarrhea, which is a known side effect of mycophenolate, can make its use in clinical practice difficult, since

it can add to the diarrheal effect of antiretroviral drugs and the disease itself in these patients. Despite the growing need for the association between immunosuppressants and antiretrovirals in current clinical practice, there are still few studies to guide the safe use of these drugs in combination.

CONCLUSION

This study achieved its objective, as it presented the main considerations about kidney transplantation in people living with HIV, according to the relevant scientific databases, following a systematic and fundamentally elaborate methodological path. It was evidenced through the collections that the presence of positive serology for HIV is no longer an absolute contraindication for kidney transplantation, being currently considered a relative contraindication. Despite this, there are still few reports of transplants in this population today. In summary, although some studies show a trend towards higher graft rejection rates in HIV-positive patients, data in the literature suggest that renal transplantation, following patient selection criteria, seems to be a safe alternative as renal replacement therapy in this group. It is expected that new and future research can emerge in relation to the proposed theme, so that the fundamental databases for the research can come to leverage the theme in question and provide the academic community with a clearer, legal and evident content. for the fullness of scientific approach.

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