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Pharmacotherapeutic Interventions in People Living With HIV Undergoing Solid Organ Transplantation: A Scoping Review

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Background. The pharmacotherapeutic management of people living with HIV (PLWHIV) undergoing solid organ transplantation (SOT) is clinically challenging, mainly due to the frequent occurrence of complex drug–drug interactions. Although various strategies have been proposed to improve treatment outcomes in these patients, several uncertainties remain, and consensus practice guidelines are just beginning to emerge. The main objective of this scoping review was to map the extent of the literature on the pharmacotherapeutic interventions performed by healthcare professionals for PLWHIV undergoing SOT. **Methods.** We searched Medline, Embase, and the Cochrane databases as well as gray literature for articles published between January 2010 and February 2020. Study selection was performed by at least 2 independent reviewers. Articles describing pharmacotherapeutic interventions in PLWHIV considered for or undergoing SOT were included in the study. **Results.** Of the 12 599 references identified through our search strategy, 209 articles met the inclusion criteria. Results showed that the vast majority of reported pharmacotherapeutic interventions concerned the management of immunosuppressive and antimicrobial therapy, including antiretrovirals. Analysis of the data demonstrated that for several aspects of the pharmacotherapeutic management of PLWHIV undergoing SOT, there were differing practices, such as the choice of immunosuppressive induction and maintenance therapy. Other important aspects of patient management, such as patient counseling, were rarely reported. **Conclusions.** Our results constitute an extensive overview of current practices in the pharmacotherapeutic management of SOT in PLWHIV and identify knowledge gaps that should be addressed to help improve patient care in this specific population.

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Although HIV infection was long considered a contraindication for solid organ transplantation (SOT), people living with HIV (PLWHIV) are now routinely accepted as potential organ recipients in specialized transplantation centers.[1,2] Accumulating evidence indicates that in the modern transplant era, HIV-infected and noninfected kidney, liver, and heart recipients have comparable survival rates.[3-5] Despite these encouraging results, recent reports suggest that PLWHIV are still less likely to access transplant waiting lists and receive an organ transplant.[6,7] Moreover, the pharmacotherapeutic management of these patients remains challenging and typically requires the participation of multiple healthcare providers to ensure the selection of optimal treatment and follow-up strategies.[8]

SOT in PLWHIV is complex for multiple reasons. Several authors suggest that the rate of acute rejection is higher in HIV-infected kidney and liver recipients.[9-12] Although a variety of factors may explain this phenomenon, difficulties in achieving optimal antiretroviral (ARV) and immunosuppressive (IS) concentrations in the context of complex drug–drug interactions has been identified as an important contributor.[9,13,14] Other specific issues among this population include a potentially higher risk of opportunistic infections (OI), and the unknown impacts of long-term IS therapy on HIV disease.[15,16]

Even with a growing body of literature on SOT in PLWHIV, several important questions remain regarding key aspects of pharmacotherapeutic management in this population.[17,18] For example, optimal treatment choices have yet to be clearly defined for induction and maintenance IS therapies.[10,19] There is also a lack of consensus on the management of ARV therapy and post-transplant antimicrobial prophylaxis for these patients and on indications for therapeutic drug monitoring (TDM).[8] Consequently, current practices appear to vary significantly between centers.[16]

Because SOT is increasingly becoming common practice in PLWHIV, assessing the evidence to support optimal pharmacotherapeutic management of this population would be highly valuable. To gain a better understanding of the current practices and identify literature gaps, we conducted a scoping review based on a specifically designed framework to map the extent of all pharmacotherapeutic interventions performed for PLWHIV considered for SOT (**Figure 1**). More specifically, the main objective of this review was to describe current pharmacotherapeutic interventions for the management of SOT in PLWHIV in terms of (1) selection and management of IS therapy; (2) management of ARV therapy and drug–drug interactions; and (3) pre- and post-transplant immunization, infection prophylaxis, and OI treatment, ultimately with the goal of identifying gaps in current knowledge.

MATERIALS AND METHODS

Study Design

Our research question was *What are the pharmacotherapeutic interventions to consider in PLWHIV undergoing SOT?* The scoping review design was chosen because we wished to generate a broad overview of the available data on the pharmacotherapeutic management of SOT in PLWHIV, without any restrictions related to study designs or outcomes. This study design aligned with our objective to map the extent and nature of the literature on the topic and identify potential knowledge gaps in a field characterized by both a rich literature and several outstanding questions. Our scoping review was conducted based on Arksey and O'Malley's[20] methodological framework, and the Joanna Briggs Institute published methodology. The results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Scoping Reviews.[21] The study protocol and Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Scoping Reviews checklist are presented as **SDC**, http://links.lww.com/TXD/A499.

Concept

In this scoping review, the term pharmacotherapeutic intervention refers to any documented action that is (i) initiated by healthcare providers and (ii) related to pharmacotherapy. Our definition of pharmacotherapeutic interventions and their relevance in the pharmaceutical care of SOT recipients were based on the American Society of Health-System Pharmacists Guidelines on Pharmacy Services in Solid Organ Transplantation and HIV Care[22] and recent reviews on the management of SOT in PLWHIV.[8,23,24] All described interventions and recommendations for practice regarding drug therapy management were considered as pharmacotherapeutic interventions. More specifically, interventions on drug therapy for HIV, transplantation and SOT-related infectious and noninfectious complications were extracted based on a predefined framework (Figure 1). The framework follows a chronological order presenting a patient pathway from pretransplant assessment through long-term follow-up post-transplant.

The main types of interventions identified were pretransplant pharmacological evaluation, prescription of induction and maintenance IS therapy, adjustment of medications based on drug interactions and TDM, prescription of OI prophylaxis and treatment, drug-related patient counseling, short and long-term follow-up, and management of graft-associated complications. Comprehensive definitions of the type of interventions are reported in **Appendix I, SDC**, http://links.lww.com/TXD/A499. Interventions were further classified according to whether they took place before or after the transplant.

Literature Search Strategy

The search strategy was developed in consultation with an information specialist. Briefly, we conducted a literature review on the Medline, Embase, and Cochrane databases using keywords including: "Human Immunodeficiency Virus," "HIV," "highly active antiretroviral therapy," "solid organ transplantation," "graft recipient," and "graft survival." The grey literature was also searched using the TRIP and NICE evidence databases, OpenGrey and clinicaltrials.gov. We chose 2010 as the onset date to ensure that the identified interventions would represent the prevailing highly active antiretroviral therapy era practices. Databases were all searched on February 21, 2020. The full database search strategy is provided as **SDC**, http://links.lww.com/TXD/A499.

Study Selection

To be included in this scoping review, articles had to meet the following inclusion criteria: (1) they were published in French or English; (2) the population included PLWHIV at least 18 y of age undergoing pre-SOT assessment or being SOT recipients; (3) the articles describe pharmacotherapeutic interventions taking place in a hospital or ambulatory

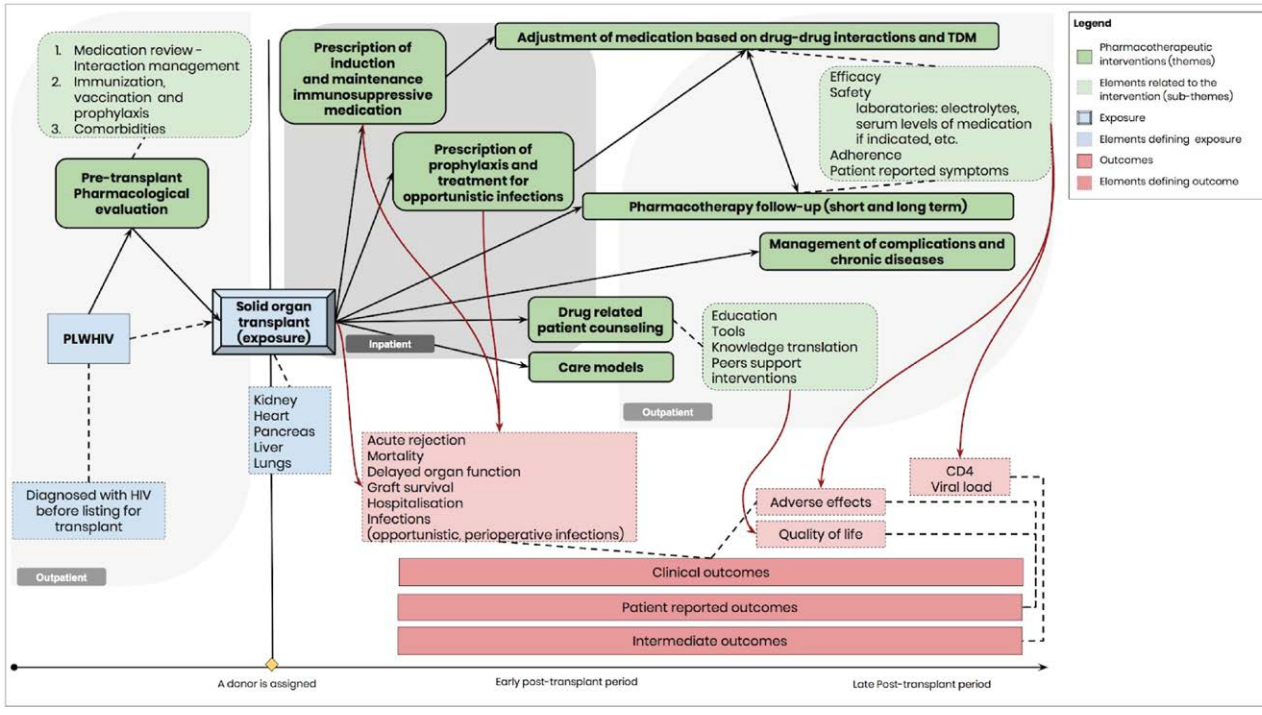

FIGURE 1. Pharmacotherapeutic interventions of solid organ transplantation in PLWHIV. The central element of this framework in blue is the exposure defined as the solid organ transplantation, green boxes illustrate pharmacotherapeutic intervention themes distributed on a time axis and red boxes represent graft-related clinical outcomes. PLWHIV, people living with HIV.

care setting. We aimed to collect a wide array of pharmacotherapeutic interventions, including those tailored to special populations (eg, patients with comorbidities such as viral hepatitis). Articles were excluded if they (1) focused primarily on surgical techniques; (2) only described social, psychological, legal, or economic aspects of SOT; (3) only described SOT outcomes (eg, survival rates, graft loss, etc); (4) did not specifically associate the pharmacotherapeutic intervention to PLWHIV when the population also contains HIV-negative recipients; and (5) described bone marrow or stem cell transplant. Narrative reviews were excluded unless they contained new unpublished clinical data. Conference abstracts were excluded.

All retrieved references were managed using the systematic review web-based software Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Each reference was screened twice for eligibility based on title and abstract by 2 independent reviewers (G.M., D.S., or G.V). Selected articles were subsequently screened based on full-text review by 2 reviewers (C.L., S.L., or D.S.). Disagreements were either resolved by consensus or by a third reviewer. The number of potentially relevant articles identified through our search was 542, which was larger than expected. A committee of experts in chronic viral illnesses and transplantation was consulted (K.M., N.S., and B.L.), and it was decided to exclude articles published before 2010 (date threshold previously set at 1996) to focus on current practices.

Data Collection and Analysis

Based on the general themes identified in the framework, a tested comprehensive extraction tool was created specifically for this review to capture all pharmacotherapeutic interventions (**SDC**, http://links.lww.com/TXD/A499). Data collection was performed by 3 reviewers (C.L., D.S., and G.V.) and a fourth reviewer (S.L.) reviewed data extraction accuracy and consistency in a random set of articles (25%). The following components were extracted for each article: authors, citation, country, type of article, objectives, interventions and control groups/comparators, population, methodology, inclusion/exclusion criteria, financial support, and pharmacotherapeutic interventions. In addition, when specified, we extracted the type of healthcare provider initiating the intervention and the intervention's impact. Each extraction followed a 2-step procedure: (1) data were collected in a Microsoft Word extraction table (narrative format); (2) collected data were coded into a Microsoft Excel sheet (prespecified subcategory). Then, we conducted a descriptive analysis of each category's and subcategory's relative frequencies to identify literature extent and research gaps. Graphs were created using GraphPad Prism (GraphPad Prism version 8.4.3 for macOS, GraphPad Software, San Diego, CA, www.graphpad.com).

RESULTS

The database searches yielded 12 599 references from database and grey literature. After excluding 3676 duplicates, 8923 articles were screened for eligibility based on titles and abstracts, and 1691 full-text articles were reviewed (Figure 2). A total of 209 articles were included in the scoping review (Figure 2). Among the articles included in the review, case reports (74/209 articles, 35.4%) and case series (42/209 articles, 20.1%) were the most frequent article types, and no randomized controlled trial met the inclusion criteria (Table 1). In addition, 7 recent guidelines were published specifically

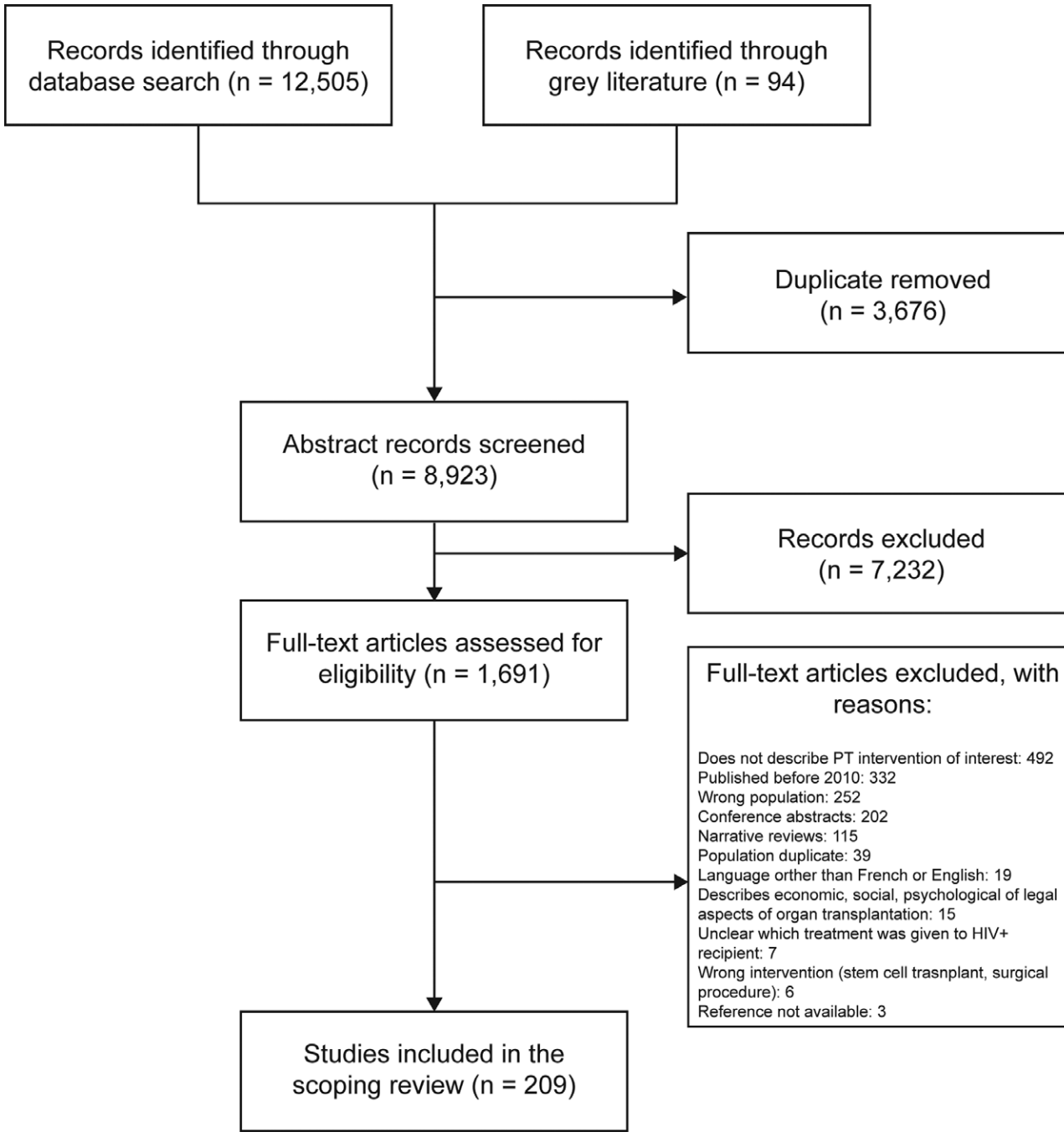

FIGURE 2. PRISMA diagram of article selection process. Selected articles were those describing pharmacotherapeutic interventions related to the management of antiretrovirals and immunosuppressive therapy, prevention and management of complications of solid organ transplantation, prevention and treatment of infections, management of drug–drug interactions, therapeutic drug monitoring and drug-related patient counseling. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PT, pharmacotherapeutic.

on PLWHIV undergoing SOT, with only 4 based on a systematic review (Table 2). Most articles concerned either kidney (107/209 articles, 51.2%) or liver transplant (70/209 articles, 33.5%). A large proportion of these articles included at least 1 hepatitis C virus (HCV) (111/209 articles, 53.1%) or hepatitis B virus (71/209 articles, 34.0%)-coinfected patient in their study population. Characteristics of the articles included in the scoping review are presented in Table 1. The list of the 209 included references is included in the **SDC**, http://links.lww.com/TXD/A499.

The extraction process allowed us to identify a total of 2348 pharmacotherapeutic interventions. The number of interventions in each predetermined subgroup is presented in Figure 3. We observed that interventions related to the choice of induction and maintenance IS therapy (827/2348 interventions, 35.2%), immunization, prevention, and treatment of infections (519/2348 interventions, 22.1%), and ARV review and therapy adjustment (288/2348 interventions, 12.3%) were the most reported in the literature (Figure 3A). These themes were particularly predominant in the interventions preceding SOT, whereas a greater number and variety of interventions were reported for post-transplantation management (Figure 3B).

TABLE 1.

Characteristics of the articles included in the scoping review

Characteristic	Variables	N = 209	%
Continent	Europe	109	52.1
	Americas	85	40.7
	Asia	10	4.8
	Africa	4	1.9
	Australia	1	0.5
Type of articles	Case reports	74	35.4
	Case series	42	20.1
	Observational prospective	21	10.0
	Descriptive, retrospective	21	10.0
	Guidelines	16	7.7
	Case-control, retrospective	13	6.2
	Retrospective cohort	7	3.3
	Expert opinion	7	3.3
	Systematic review/Meta-analysis	4	1.9
	Interventional, prospective	3	1.4
	Survey	1	0.5
Organ transplant	Kidney	107	51.2
	Liver	70	33.5
	Mixed population/multiple organs	17	8.1
	Heart	9	4.3
	Lung	3	1.4
	Pancreas	1	0.5
	General/ unspecified	4	1.9
Recipient status	HCV+[a]	111	52.6
	HBV+[b]	71	34.0
Donor status	HIV+[c]	10	4.8

[a]Number of studies that study population included at least 1 HCV/HIV-coinfected patient.
[b]Number of studies that study population included at least 1 HBV/HIV-coinfected patient.
[c]Number of studies that study population included at least 1 HIV+ donor.
HBV, hepatitis B virus; HCV, hepatitis C virus.

Overall, the vast majority of interventions related to drug or vaccine prescription and monitoring, whereas very few interventions concerned medication-related counseling (8/2348 interventions, 0.34%). The identity of healthcare providers performing the interventions was only reported in 5.1% (120/2348) of the interventions.

Pharmacotherapeutic interventions were classified into subgroups and ranked by their relative occurrences (Figure 4). The most frequent theme concerned the choice and management of IS therapy. Our results indicate that calcineurin inhibitors (CIs) and antimetabolites are routinely prescribed or recommended for maintenance immunosuppression (Figure 4B). Corticosteroids are also frequently part of the maintenance regimen, although several references reported the use of a corticosteroid-sparing regimen (8/209 articles). There was more variability in the choice of induction therapy (Figures 4A and 5). Anti-interleukin-2 receptor antibodies (anti-IL-2R) were the most recommended or chosen agents as part of the induction therapy (n = 97), followed by antithymocyte globulin (ATG) (n = 45) and high-dose intravenous corticosteroids (n = 40). When interventions for kidney and liver transplantation were compared, we observed that anti-IL-2R were more frequently used than ATG for both, whereas anti-CD52 use was only reported in kidney transplant (Figure 5).

Prevention and treatment of infectious complications was another prominent theme of reported pharmacotherapeutic interventions (Figure 4C). A majority of these interventions comprised prophylaxis for bacterial, viral, and fungal infections, with no specific indication that antimicrobial prophylaxis significantly differed from what is routinely used in HIV-negative organ recipients. The most common HIV population–specific prophylaxis-related intervention was to prescribe lifelong *Pneumocystis jirovecii* prophylaxis (n = 16). Some authors specifically suggested using the same antimicrobial prophylaxis as in HIV-negative recipients (n = 7). Management of HCV was also a frequent topic within this group (n = 65), with most interventions addressing pre- or post-transplant treatment and the management of recurrence in both kidney and liver transplant.

A large number of interventions were related to the management of ARV therapy and drug–drug interactions (Figure 4D and E). A frequently reported recommendation was to continue ARVs until SOT and restart postoperatively. Our results indicate that ritonavir and cobicistat-boosted regimens are commonly avoided and that integrase strand transfer inhibitor-based (InSTI) regimens are preferred. Adjustment of ARV therapy in the early post-transplant period was often reported, with the main intervention being ARV dose increase for improved kidney function postkidney transplant. Immunosuppressant doses were adjusted based on TDM. Unsurprisingly, several authors recommend more frequent monitoring. On the other hand, adjustment of ARV dosing based on TDM was seldom reported (n = 3). Drug interactions resulting in dose adjustments were most commonly seen with coadministration of CIs (n = 45) and protease inhibitors (PIs) (n = 42). Dose modifications were also required because of drug interactions involving non-nucleoside reverse transcriptase inhibitor (NNRTIs) (n = 6), mammalian target of rapamycin inhibitors (n = 3) and antimetabolites (n = 1). Adjustments and modifications of ARV therapy to avoid interactions with HCV antiviral drugs were also prevalent (n = 19).

Other post-transplantation follow-up interventions mainly consisted of CD4+ and viral load monitoring (Figure 4F), without clear recommendations on testing frequency in most cases. Monitoring of tolerability to IS therapy was also frequent, with CI-induced nephrotoxicity being the most reported adverse event.

Organ rejection was most commonly managed by initiating new therapy (n = 106). The most widely reported therapies were intravenous corticosteroids, ATG, and plasmapheresis (Figure 4G). Doses of maintenance IS agents were also frequently increased in response to acute rejection (n = 33). Other than organ rejection, malignancy was a common reason for modifying IS therapy (Figure 4G). Kaposi sarcoma was the main reported cancer requiring adjustment or modification of IS therapy (n = 15).

DISCUSSION

In this scoping review, we collected a wide range of pharmacotherapeutic interventions performed or recommended for PLWHIV undergoing SOT. Overall, our results confirm the complexity of medication management in this population and underline a significant variability in suggested treatment strategies. We note that the most abundant articles were case reports and case series, implying that SOT in PLWHIV is still not standard practice in many centers. As expected, the choice of IS agents and management of drug–drug interactions

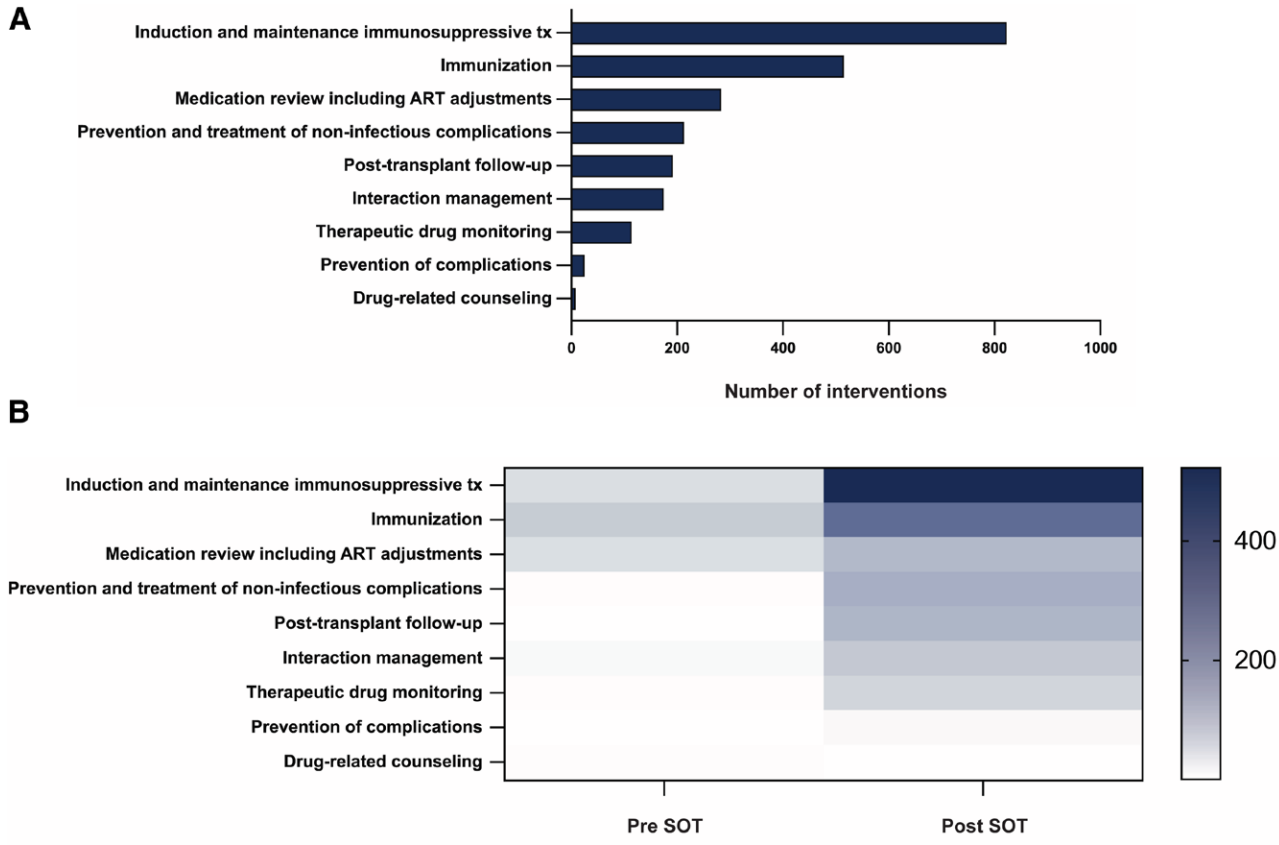

FIGURE 3. Number of pharmacotherapeutic interventions by categories. A, Number of pharmacotherapeutic interventions after classification in subgroups. B, Number of pharmacotherapeutic interventions by categories pre- and postsolid organ transplantation (only interventions for which this information was available are represented). ART, antiretroviral therapy; SOT, solid organ transplantation; tx, transplantation.

between IS and ARV agents are among the most reported interventions we found.

Our results demonstrate the existence of a consensus to avoid PI-based regimens and to opt for InSTI-based ARV regimen whenever possible.[8,27,32,33] A recent retrospective study of HIV-infected kidney transplant recipients confirmed that higher rejection rates are observed in patients receiving PI-based regimens.[34] In addition, NNRTIs significantly affecting cytochrome P450 enzymes, such as efavirenz, are also frequently avoided.[35-37] Most authors preferred using the first approved InSTI raltegravir.[26,33] Recent guidelines also recommend dolutegravir-based regimens, in recognition that it has a high genetic barrier to resistance and a low potential for drug interactions.[38] One potential drawback, however, is the inhibition of creatinine renal secretion by dolutegravir through OCT-2 transporter inhibition, which complicates renal function monitoring in kidney transplant patients.[39] More data will be required to determine which InSTI provides the best efficacy, safety, and tolerability profile in this subpopulation.[40] In this regard, an ongoing study aims to evaluate the feasibility of switching HIV-infected kidney transplant recipients to a 3-drug fixed-dose combination containing bictegravir, tenofovir alafenamide, and emtricitabine (NCT04530630).

Our results also highlight the difficult task of managing drug interactions in patients treated with PI- or NNRTI-containing regimen.[41,42] We observed a striking variability in proposed strategies to achieve target levels of IS agents in the context of drug–drug interactions between IS agents and PIs or NNRTIs. For example, to manage interactions between IS and ritonavir-boosted ARV regimens, some authors reported a 99% tacrolimus dose reduction,[25,43] whereas others have suggested an increase in tacrolimus dosing interval[44] or a combination of both approaches.[45,46] Some authors recommend a pre-SOT immunosuppression trial with frequent TDM to establish patient-specific optimal dosing for IS agents.[47,48] Overall, this suggests that optimal IS drug dosage vary considerably between individuals in the context of drug interactions with NNRTIs and PIs, which may explain the lack of precise dosing recommendations. In addition, other significant interactions between non-ARV drugs (eg, azoles) and immunosuppressants can further complicate dose adjustment. Nonetheless, recent guidelines provide essential guidance on starting dose ranges for some IS agents when combined with boosted PIs[8] and a few studies have evaluated the use of pharmacokinetic modeling to manage drug interactions between ARV and IS agents.[49-53] More study is also needed to improve long-term outcomes and prevent toxicity from both IS and ARV therapies. For instance, when compared with cyclosporine in HIV-infected kidney transplant recipients, the use of tacrolimus was associated with a reduced risk of acute rejection.[54]

Importantly, this scoping review also identified several persisting knowledge gaps in this young and evolving field. Our results emphasize the lack of clear consensus regarding the choice of IS induction therapy (Figure 5). This finding was also apparent when the different guidelines included in our scoping review were compared (Table 2). Anti-IL-2R antibody use was more commonly reported than ATG. An

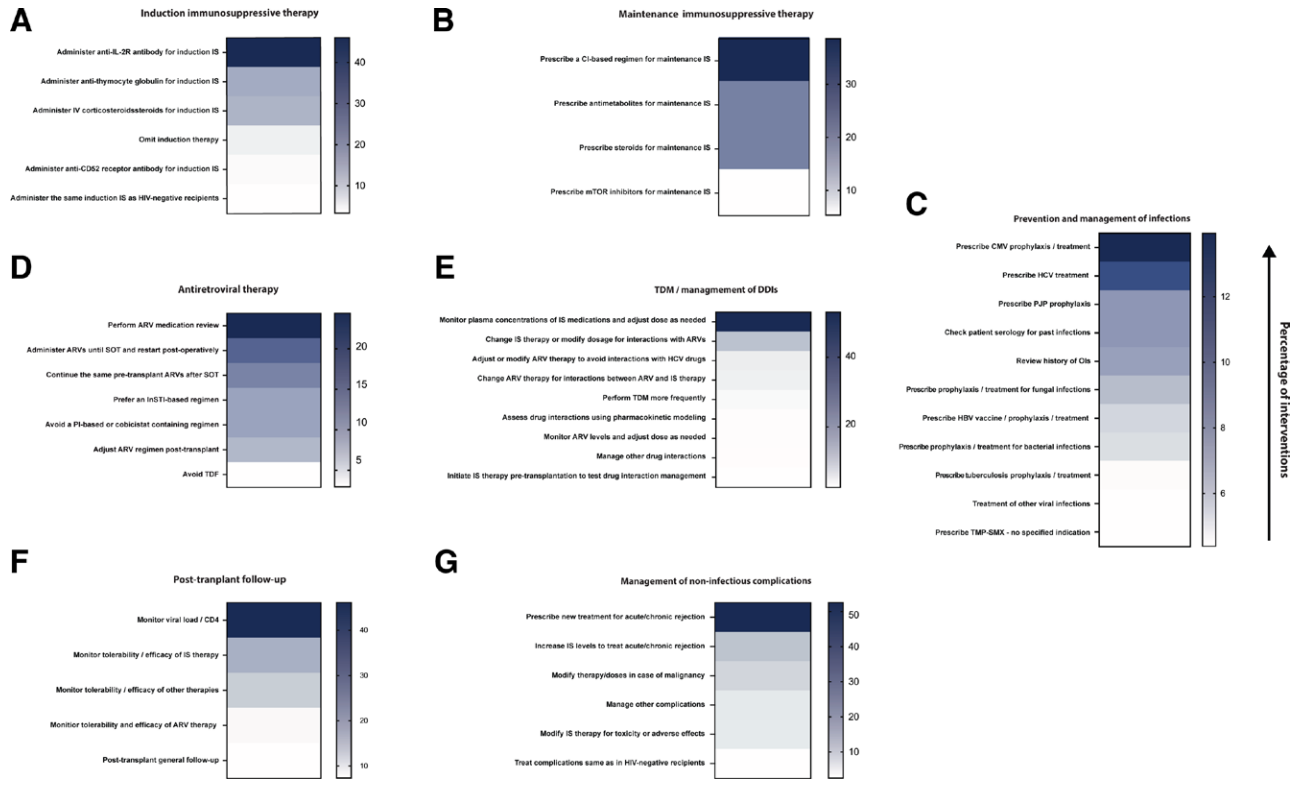

FIGURE 4. Percentage of pharmacotherapeutic interventions by subgroups. Heat maps represent the frequency of pharmacotherapeutic interventions as the percentage of the total number of interventions collected in each of the following categories: induction and maintenance of immunosuppression therapy (A and B), prevention and management of infections (C), ARV therapy (D), therapeutic drug monitoring/management of DDI (E), post-transplant follow-up (F), and management of noninfectious complications (G). Interventions that represented a minimum of 2% of all interventions in each subgroup are shown in the graph. Anti-IL-2R, anti-interleukin-2 receptor; ARV, antiretroviral; CI, calcineurin inhibitor; CMV, cytomegalovirus; DDI, drug–drug interactions; HBV, hepatitis B virus; HCV, hepatitis C virus; InSTI, integrase strand transfer inhibitor; IS, immunosuppressive; IV, intravenous; mTOR, mammalian target of rapamycin; NNRTI, nonnucleoside reverse transcriptase inhibitor; OI, opportunistic infection; PI, protease inhibitor; PJP, *Pneumocystis jirovecii* pneumonia; SOT, solid organ transplantation; TDF, tenofovir disoproxil fumarate; TDM, therapeutic drug monitoring; TMP-SMX, trimethoprim-sulfamethoxazole.

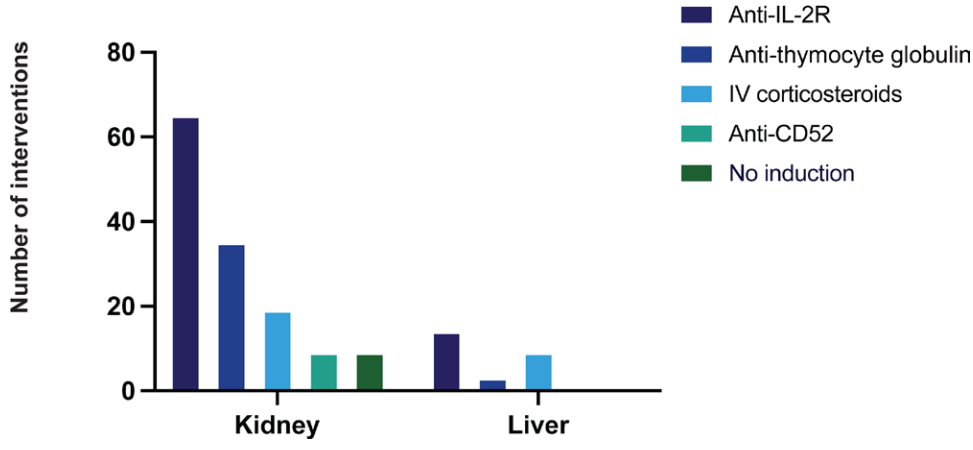

FIGURE 5. Pharmacotherapeutic interventions describing the use of immunosuppressive agents for induction therapy in kidney and liver transplant. The total number of pharmacotherapeutic interventions reporting the use of immunosuppressive agents for induction therapy are presented for each agent. Anti-IL-2R, anti-interleukin-2 receptor antibodies; IV, intravenous.

important study by Locke et al[10] showed that the frequently reported higher risk of acute rejection in HIV-infected kidney recipients was not observed in patients receiving ATG induction. However, this is still an area of debate[19] and some have expressed concerns about the potential increased risk of infection and malignancy in patients receiving lymphocyte-depleting therapy.[55] Previous results have indeed highlighted that ATG can effectively reverse rejection in HIV-infected kidney recipients, but this may come at the cost of an increased risk of severe infections and hospitalizations.[56] In this context, current guidelines recommend using ATG for induction therapy in high immunological risk candidates.[8,26] Alemtuzumab, an anti-CD52 antibody, has been used as induction therapy in HIV-infected kidney transplant recipients,[57] and its use may

TABLE 2.

Recommendations from most recent guidelines on the management of solid organ transplantation in people living with HIV

Authors Organism	Organ transplant	Year	Induction immunosuppression	Maintenance immunosuppression	Antiretrovirals	Therapy adjustments
Lucas et al[25] Infectious Diseases Society of America	Kidney	2014	–	–	Consider switching to a raltegravir-based regimen	Close TDM of tacrolimus, cyclosporine, and sirolimus with dose adjustments
AIDS Working Group (GESIDA), Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Spanish Society of Nephrology (SEN), Spanish Society of Clinical Chemistry and Molecular Pathology (SEQC)[26]	Kidney	2014	Basiliximab ATG/rATG in patients with high immunological risk (reduced doses)	Tacrolimus with mycophenolate mofetil and corticosteroids	Prefer ABC or TDF with 3TC or FTC with raltegravir or dolutegravir	Adjust doses of IS drugs (cyclosporine, tacrolimus, sirolimus, and everolimus) if PIs or NNRTIs must be used. Close lymphocyte monitoring if using ATG/rATG
The British Transplantation Society[27]	Kidney and pancreas	2015	Anti-IL-2RA	Triple therapy with CI, antiproliferative agent, and steroids	Avoid boosted PI-based regimens. For kidney transplant, avoid ARVs with nephrotoxic potential	Dose-finding trial of CIs before SOT
Miro et al[28] European Association for the Study of the Liver	Liver[a]	2015	–	–	Prescribe PI-sparing regimen. Combination of 2 NRTIs plus raltegravir preferred	Frequent monitoring of IS drug levels if PIs are necessary. TDM of CI is indicated in all HCV/HIV coinfected liver recipients
Terrault et al[29,30] International Liver Transplantation Society	Liver[a]	2017	–	–	Avoid PI-based regimens	IS drug levels monitored carefully (every 2 wk) during and for 3 mo post-treatment in HIV/HCV-coinfected patients. Adjust IS drug doses to maintain levels in target ranges
Ryom et al[31] European AIDS Clinical Society	No specific organ	2018	Same as HIV-negative recipients	Same as HIV-negative recipients	Prefer raltegravir (or dolutegravir) plus 2 NRTIs. Avoid ritonavir, cobicistat, and some NNRTIs (NVP, EFV, and ETV)	Close monitoring of IS regimen
Blumberg and Rogers[8] American Society of Transplantation	No specific organ	2019	Lymphocyte depletion or anti-IL-2RA. Lymphocyte-depleting induction for high immunological risk candidates	Tacrolimus, mycophenolate analog, and long-term corticosteroids.[b] Avoid steroid-free regimens	Avoid PI- or cobicistat-based regimens. Prefer InSTI-based regimens. Prefer TAF to TDF	If a boosted PI is necessary, dose reductions of CIs and mTOR inhibitors are required. Daily monitoring of levels is required to determine optimal dosing

[a]Guidelines specific to HIV/HCV-coinfected patients.
[b]Kidney transplant.
ABC, abacavir; ARV, antiretroviral; ATG/rATG, antithymoglobulin/rabbit antithymoglobulin; CI, calcineurin inhibitor; EFV, efavirenz; ETV, etravirine; FTC, emtricitabine; HCV, hepatitis C virus; IL2RA, anti-interleukin-2 receptor antibodies; InSTI, integrase strand transfer inhibitor; IS, immunosuppressant; mTOR, mammalian target of rapamycin; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; SOT, solid organ transplantation; TAF, tenofovir alafenamide; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate; TDM, therapeutic drug monitoring.

be of particular interest for high immunological risk patients. Importantly, our results also highlight the absence of additional specific indications regarding antimicrobial prophylaxis in PLWHIV undergoing SOT. The sole HIV population–specific intervention identified in our study was the lifelong *Pneumocystis jirovecii* prophylaxis, which was recommended in the HIV-TR study.[9] Altogether, these observations suggest that additional studies are required to better characterize the clinical response to IS induction therapies and propose individualized treatment and prophylaxis approaches relying on clinical evidence for PLWHIV.

Interestingly, our extensive literature review yielded a very limited number of reports on interventions regarding patient counseling or therapy adherence and tolerability monitoring. In addition, those interventions were rarely specific in terms of follow-up indicator and frequency. Treatment adherence is crucial to ensure favorable outcomes in transplanted patients, and nonadherence is associated with an increased risk of allograft loss.[58] Continuous treatment adherence to antiretrovirals to prevent virological failure and resistance of HIV is a challenge in many PLWHIV. The added burden of IS therapy conceivably represents an additional barrier to treatment adherence. Therefore, it is surprising that we did not find a significant number of interventions describing or addressing this aspect of treatment management. Furthermore, the healthcare professionals involved in the pharmacotherapeutic interventions were rarely specified. Therefore, it is seemingly difficult to propose a patient care protocol solely based on the information found in the literature. Involving a multidisciplinary team was reported, but the available literature does not provide guidance on the team members and the benefits of their involvement early on. Research aimed at evaluating the impact of treatment counseling, adherence monitoring, and multidisciplinary interventions in PLWHIV undergoing SOT may prove to be important in optimizing treatment outcomes.

A large proportion of articles in our scoping review included HIV/HCV-coinfected patients. Outcomes of liver transplantation were previously reported to be poorer in the HIV/HCV-coinfected population compared with HIV monoinfected individuals,[59] with most articles published before direct-acting antiviral (DAA) use. Current evidence suggests that DAA are effective and well tolerated in this specific group.[60] However, because DAA can interact with ARVs and immunosuppressants,[61] HCV coinfection undoubtedly adds another layer of complexity to drug therapy management. This was reflected in our results by numerous interventions related to HCV treatment (Figure 4C and E). These results highlight the importance of consulting with an HIV and HCV expert to manage coinfected patients,[29] especially in cases where changes to ARV therapy and selection of HCV therapy may be required.

Our study is not without limitations. First, by definition, our scoping review does not allow us to conclude on the effectiveness of the pharmacotherapeutic interventions found. A standardized approach to advise on a SOT program in PLWHIV would have to include a careful review of the evidence for the considered interventions. Second, our definition of pharmacotherapeutic interventions comprised both reported interventions and recommended practices. Although this approach allowed us to assemble a more exhaustive list of relevant references for healthcare professionals, it also paints a less accurate picture of current clinical practices. Indeed, it is unclear if recent guideline recommendations are currently implemented in specialized transplantation centers or if more center-specific approaches are routinely favored. Third, some pharmacotherapeutic interventions that are routinely done in SOT patients' evaluation are likely underrepresented in our results. This was however expected, because many articles that were included in our study were focused on HIV-specific issues. Fourth, our review included only articles published since 2010, although data reported before may still represent or influence current practices. However, the impact of older studies that helped define the optimal management of SOT in PLWHIV would likely influence the most recent literature and practices. Finally, although the scoping review design presents the advantage of collecting a large amount of information on pharmacotherapeutic interventions performed in our population of interest, we did not evaluate the quality or risk of bias of the studies included in our review.

Our findings hold implications for the direction of future clinical research on SOT in PLWHIV. Indeed, this scoping review sheds light on several aspects of medication management that require further clarifications. With the available data mostly consisting of case reports and case series, a systematic review and meta-analysis on the choice of ARV or induction IS regimen would probably not be conclusive. Also, pharmacokinetic monitoring and modeling studies may prove to be particularly beneficial in the management of drug–drug interactions that may affect plasma concentrations, efficacy, and safety of IS drugs.[62] Finally, larger clinical trials in PLWHIV who undergo SOT would provide more guidance to develop care pathways to help optimize care and prevent adverse outcomes.

CONCLUSION

In summary, the results from our scoping review suggest that despite the increasing number of articles reporting on the pharmacotherapeutic management of SOT in PLWHIV, several areas of uncertainties remain to be elucidated. This scoping review may not only serve as a tool to design future research but may also guide future efforts to develop more comprehensive practice guidelines to improve drug management in this complicated population.

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