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REVIEW

# Effects of immunosuppressive drugs on HIV infection: implications for solid-organ transplantation

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## Summary

With the advent of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease. Various end-stage organ failures have now become common co-morbidities and are primary causes of mortality in HIV-infected patients. Solid-organ transplantation therefore has been proposed to these patients, as HIV infection is not anymore considered an absolute contraindication. The initial results of organ transplantation in HIV-infected patients are encouraging with no differences in patient and graft survival compared with non-HIV-infected patients. The use of immunosuppressive drug therapy in HIV-infected patients has so far not shown major detrimental effects, and some drugs in combination with HAART have even demonstrated possible beneficial effects for specific HIV settings. Nevertheless, organ transplantation in HIV-infected patients remains a complex intervention, and more studies will be required to clarify open questions such as long-term effects of drug interactions between antiretroviral and immunosuppressive drugs, outcome of recurrent HCV infection in HIV-infected patients, incidence of graft rejection, or long-term graft and patient survival. In this article, we first review the immunological pathogenesis of HIV infection and the rationale for using immunosuppression combined with HAART. We then discuss the most recent results of solid-organ transplantation in HIV-infected patients.

## Introduction

The year 2006 marked the 10th anniversary of the introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV infection. Ten years of powerful combinations of antiretroviral drugs have completely changed the natural outcome of HIV infection and dramatically improved survival of HIV-infected patients, making HIV infection mostly a controllable chronic infection.

With HAART, fewer patients are dying of opportunistic infections or other acquired immuno-deficiency syndrome (AIDS)-related diseases [1–3]. A recent data estimate about the benefit gained with antiretroviral combinations showed that at least 3.0 million years of life have been saved in the United States as a direct result of antiretroviral treatment [4]. In the United States, AIDS was the first cause of death in men and women of 25–44 years old, between 1992 and 1994, over accidents, cancer and heart disease, with a sharp fall in mortality because of AIDS, following the introduction of HAART [5]. In recent years, opportunistic infections have been replaced by chronic kidney, liver and cardiac disease as leading causes of mortality in HIV-infected patients on HAART [6]. Chronic illnesses commonly encountered in HIV-infected patients, such as co-infection with hepatitis C and B viruses (HCV; HBV), are emerging as principal causes of morbidity and mortality.

The routes of transmission for HIV, and HCV and HBV are similar and consequently, co-infection with HIV

 

is very frequent. In Western countries, it is estimated that in HIV-infected patients, the prevalence of co-infection with HBV is about 6–8% [7] and with HCV about 35% [8,9]. The prevalence of co-infection varies depending on the epidemiology, reaching 90% of co-infection of HIV–HCV in intravenous drug users and haemophiliacs [8,10,11]. In co-infected patients, the course of hepatitis C has been shown to be more rapid and aggressive, compared with non-HIV-infected individuals [12]. Moreover, advanced liver disease has become a leading cause of death among HIV–HCV and HIV–HBV co-infected patients [13,14]. Co-infection with HIV also accelerates occurrence of hepatocellular carcinoma, compared with non-HIV-infected individuals [15,16]. Finally, HAART may accelerate deterioration of liver function, as the majority of antiretroviral drugs are associated with some degree of hepatotoxicity [17–21].

Recently, end-stage renal disease (ESRD) was shown to be increased among HIV-infected patients. Renal disease can be directly related to HIV infection, as in HIV-associated nephropathy (HIVAN), or due to immune-complex glomerulonephritis, to antiretroviral drug nephrotoxicity, or to other common causes such as diabetes and hypertension [22–24]. HIVAN currently represents the third leading cause of ESRD in young African-Americans [25,26], and dialysis and/or renal transplantation represent the only therapeutic options.

Transplantation of HIV-infected patients with its subsequent immunosuppression has raised concerns about decompensation of stable patients under HAART with the possibility of increasing viral replication and decreasing CD4 cell counts with subsequent risks of opportunistic infections and malignancies. Thus, solid-organ transplantation was considered, until recently, as a contraindication in HIV-infected patients [27].

In the recent years, however, some centres performed solid-organ transplantation in HIV-infected patients with satisfactory and promising results regarding graft and patient survival, and without acceleration of HIV infection. Several studies in the HAART era have shown that patient and graft survival rates after transplantation are similar to non-HIV-infected recipients [28,29].

In this article, we first focus on the pathogenesis of HIV infection and the rationale for using immunosuppression coupled with HAART. We further discuss the possible beneficial impacts of immunosuppression on HIV infection. Finally, we review the most recent results of solid-organ transplantation in HIV-infected patients.

## HIV immunopathogenesis

The natural history of HIV infection is characterized by a progressive depletion with functional abnormalities of CD4 T lymphocytes that causes the profound immunosuppression which is characteristic of AIDS [30].

The typical course of HIV infection starts with an early phase, where primary HIV infection (PHI) is followed by a spread dissemination of the virus with a sharp decrease in the number of CD4 T cells in peripheral blood. PHI is characterized by a high level of viral replication with dissemination of the virus to all organs and in particular to 'viral reservoirs' (lymphoid organs).

Human immunodeficiency virus induces a persistent state of immune activation that drives to the exhaustion of T-cells specific functions as well as to apoptosis (programmed cell death). HIV is able to infect both resting and activated CD4 T cells, but it replicates only in activated CD4 T cells [31].

The early phase of the infection is characterized by the generation of HIV-specific humoral and cellular immune responses. The appearance of the virus-specific immune response is associated with a decrease of viremia. Following the generation of HIV-specific immune responses, a long period of clinical latency is observed (median: 10 years). During this period, patients are asymptomatic until a critical level of circulating CD4 T cells is reached (CD4 T-cell count is below 200 cells/$mm^3$) [32]. Below 200 CD4 T cells/$mm^3$, the risk for opportunistic infections substantially increases.

During chronic infection, the state of immune activation persists with continuous production of pro-inflammatory cytokines (IL1, IL6, TNF), increased turnover of B and T cells and a generalized activation of T cells [33–35].

This abnormal activation of CD4 T cells favours continuous infection of more CD4 T cells, with progressive loss CD4 T cells and alteration in CD4 functions with a consequent impact on CD8 T cells, B cells and NK [32]. HIV therefore induces a vicious circle where its replication is perpetuated by immune activation that allows continuous viral replication.

The importance of immune activation in the pathogenesis of HIV infection has been elucidated by studies in monkeys such as sooty-mangabeys, which are natural hosts for the Simian Immunodeficiency Virus (SIV). Indeed, these monkeys, despite very high levels of viral replication, neither develop increased immune activation, nor an immune-deficient disease [36]. Both in the acute and chronic phase of SIV infection in sooty-mangabeys, there is no evidence for immune activation as indicated by low levels of expression of activation and proliferation markers on CD4 T cells, low levels of T-cell apoptosis and normal lymphocyte morphology [37,38].

In HIV-infected patients, effective HAART inhibits viral replication and subsequently reverts immune activation [39]. HAART results in an increased number of CD4 T

cells and partially improves functional defects of CD4 and CD8 T cells, but it is not sufficient to eradicate infection. Despite HAART, infected resting-CD4 T cells persist and can sustain viral replication in case of cellular activation [40,41].

Anti-HIV-specific CD4 T-cell proliferative responses are generally lost and HIV-specific cytotoxic CD8 T-cell clones are deleted at the time of primary infection. Because HAART alone cannot restore anti-HIV-specific immune responses that are lost in the first phase of the infection, additional strategies to HAART, such as immune-based interventions have been investigated.

The main objectives of immune-based interventions, coupled with HAART, are as follows: (i) maintenance or potentiation of existing anti-HIV specific or nonspecific immune responses, (ii) induction of *de novo* anti-HIV-specific immune responses and (iii) restoration of pre-existing HIV-specific immune responses that have been lost during HIV disease.

Overall, immune-based interventions aim at eliminating latently infected cells and at increasing HIV-specific immune responses, in order to achieve a long-term control of the infection [42].

Immune strategies aim to target the pool of latently infected cells that constitute the reservoir for replication competent virus, and also aim to reduce the number of cells that can be targets for the virus by decreasing cellular activation. Over the years, various immune-based strategies such as IL2, hydroxyurea, cyclosporin and mycophenolate mofetil (MMF) have been studied [43,44].

Some of these drugs have shown a beneficial effect on HIV replication *in vitro* and a possible beneficial impact on CD4 T-cell reconstitution *in vivo*. We will discuss below, the use of cyclosporine and mycophenolate, two current 'cornerstone' drugs of immunosuppression (IS) therapy in transplant recipients, in the HIV setting as components of antiviral therapy.

## Cyclosporin A

Cyclosporin A (CsA) is a calcineurin inhibitor (CNI) commonly used in combination with other immunosuppressive drugs in anti-rejection treatment of transplant recipients. CsA inhibits T-cell activation by interfering with IL2 synthesis. CsA exerts its effect through binding to cyclophilin (CypA), a cytoplasmic protein member of immunophilin family. The complex CsA/CypA binds calcineurin and inactivates a phosphatase activity necessary for dephosphorylation and activation of NF-AT (nuclear factor of activated T cell), thereby inhibiting T-cell activation (review in 45).

*In vitro* studies have shown that host cyclophilin A is required for HIV viral replication as HIV–Gag polyprotein forms a stable complex with cyclophilin that is essential for viral replication [46]. It has been demonstrated that different levels of expression of cyclophilin interfere in different manner with HIV replication [47]. As cyclophilin A is involved in protein folding, it associates with Gag protein, and is also incorporated into virions leading to the formation of new viral particles [48,49]. Consequently, cyclosporin can modulate HIV infectivity by forming a complex in the virion core with HIV–Gag protein, disrupting cyclophilin incorporation into virions and blocking nuclear import of HIV-DNA in activated CD4 T cells [50,51]. Furthermore, cyclosporin inhibits T-cell activation by blocking activation of the genes for IL2, IL4 and the IL2 receptor in T cells, thereby inhibiting IL2-dependent T-cell proliferation and differentiation [52].

Thus, cyclosporin can interfere with HIV through two mechanisms: directly, via inhibition of HIV replication through the interaction with Gag, and indirectly through the inhibition of T-cell activation [53]. Cyclosporin activity is lymphocyte-specific and blocks quiescent lymphocytes in phase G0–G1, thus reducing the number of cells that can be activated, supporting new rounds of HIV infection.

In 1998, we started a phase I/II study to treat patients ($n = 9$) with PHI, with HAART in combination with CsA. A control group was represented by patients with PHI, treated with HAART without CsA ($n = 29$). The study was carried out at the Division of Immunology at Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, and at the Division of Infectious Diseases at San Raffaele Scientific Institute in Milan, Italy and the preliminary results have been published [54].

The rationale to administer CsA coupled with HAART was to prevent the massive T-cell activation characteristic of PHI. HAART consisted of a combination of two nucleoside transcriptase inhibitor (NRTI) (zidovudine and lamivudine) and two protease inhibitor (PI) (nelfinavir and saquinavir soft gel). CsA was administered only in the first 8 weeks of treatment, and thereafter patients continued treatment with HAART alone. CsA was administered at a dose regimen ranging between 0.3 and 0.6 mg/kg, given orally every 12 h according to cyclosporin plasma levels (aim: cyclosporin plasma levels between 250 and 450 μg/l). Because of potential pharmacological interactions between CsA and PI, plasma levels of CsA were monitored frequently. Overall, CsA was well tolerated in all patients, and none of the patients developed opportunistic infections.

During the first days of therapy, we observed a net increase, over baseline values, in both CD4 T-cells percentage and cell count, significantly greater in patients treated with CsA and HAART, compared with patients treated with HAART alone, and this benefit was main-

 

tained also after stopping CsA (after 8 weeks of therapy). In particular, after only 7 days of therapy, the mean increase in both percentage and absolute cell count of CD4 T cells was already significantly greater in patients treated with CsA and HAART compared with patients receiving HAART alone ($P = 0.048$ and $P = 0.027$ respectively). The significant increase in CD4 T cells observed in patients treated with CsA and HAART was not associated with an expansion of the pool of proliferating CD4 T cells as measured by the intracellular level of expression of Ki-67 nuclear antigen, which stains cell on cycle. We also observed a simultaneous decrease in CD8 T cells, inducing a more rapid normalization of the CD4/CD8 ratio in patients receiving CsA + HAART compared with those receiving HAART alone. Interestingly, we did not observe any immunological detrimental effects of CsA. Functional analysis showed that both CD4 and CD8 responses HIV-specific, and immune responses against other viruses such as cytomegalovirus (CMV) and Epstein–Barr Virus (EBV) were not affected by CsA use.

Currently, the study is still ongoing, and we have enrolled an increasing number of patients with a diagnosis of PHI treated with CsA + HAART ($n = 38$) and HAART alone ($n = 43$). More recently, HAART consisted of two NRTI along with ritonavir-boosted PI (ritonavir/lopinavir) and CsA was administered always for the first 8 weeks.

We confirmed our preliminary results in this larger cohort of patients, observing a net increase over baseline values in both CD4 percentage and absolute cell count, significantly greater, in patients receiving CsA + HAART than in patients receiving HAART alone.

Moreover, the initiation of therapy induced an effective and sustained suppression of viral replication in both groups of patients, but interestingly, at week 36 of treatment, the proportion of patients attaining plasma HIV-1 RNA levels below 50 copies/ml was significantly higher in patients receiving CsA with HAART than that in patients receiving HAART alone [55].

Importantly, levels of plasma HIV-RNA measured at baseline significantly predicted changes from baseline in CD4 T cells after 2 weeks of therapy ($P = 0.022$ regression analysis), indicating that in patients receiving CsA in addition to HAART, higher levels of plasma viremia at baseline were associated with greater increase in CD4 T cells after 2 weeks of therapy.

It is important to underscore that after 8 years since the first patient was enrolled in the CsA study, we did not observe any long-term CsA-associated toxicity or any occurrence of malignancies or opportunistic infections.

Of note, Calabrese *et al.* reported the results of a placebo-controlled trial where 28 patients with chronic HIV infection were randomized to receive CsA or placebo for 12 weeks. Patients were either receiving no antiviral therapy or were on a stable regimen with only two NRTI. Contrary to our studies, they did not observe any immunological benefit in patients treated with CsA compared with patients without CsA; moreover, they observed that HIV-RNA tended to increase in patients treated with CsA [56].

The discordant results obtained in the two studies can be explained by the different patients cohorts studied, i.e. patients with primary versus chronic infection and by the two different study design, i.e. transient versus chronic treatment with CsA. It is likely that chronic treatment with CsA is associated with greater immunosuppression.

In summary, our initial clinical experience showed that CsA coupled with HAART is safe for HIV-infected patients, and it appears to confer immunological benefits, if this treatment strategy is administered during primary HIV infection.

## Mycophenolate mofetil

Mycophenolate mofetil, the ester prodrug of mycophenolic acid (MPA), is currently used in immunosuppression combinations for organ transplantation. MMF is hydrolysed to its active metabolite MPA *in vivo*. MPA is a specific inhibitor of lymphocyte proliferation, inhibiting the *de novo* synthesis of purines. MPA inhibits inosine monophosphate dehydrogenase, by blocking the conversion of inosine monophosphate to guanosine monophosphate and decreasing intracellular deoxyguanosine triphosphate pools.

MPA selectively inhibits the *de novo* synthesis of purines in T and B lymphocytes as, lymphocytes depend on the *de novo* purine synthesis and cannot use the salvage pathway for guanosine synthesis. Therefore, MPA prevents proliferation of T and B lymphocytes [57,58].

Human Immunodeficiency Virus replication is dependent on cellular deoxyribonucleoside triphosphate for transcription of viral single-stranded RNA into double-stranded DNA competent for integration and completion of viral cycle [59,60]. It has been shown that MMF suppresses HIV replication *in vitro*, and enhances antiviral activity of specific anti-HIV drugs, such as NRTI currently used in antiretroviral combinations such as abacavir [61], didanosine (ddI) and tenofovir (TFV) [62,63]. Finally, MPA is effective *in vitro* both against wild-type and NRTI-resistant HIV strains [62,63].

Margolis *et al.* [64] reported results of a small study of patients with late-stage advanced AIDS with multidrug resistance and incomplete suppression of HIV viremia, who were treated with MMF (500 mg twice a day) in addition to HAART. Overall, MMF was well tolerated and induced a decline in HIV viremia, suggesting a beneficial effect of MMF, probably because of the synergistic

effect with some NRTI, even in patients with advanced disease and multidrug-resistant HIV infection.

In contrast, Sankatsing *et al.* analysed the effect of MMF associated with HAART in 'treatment-naïve' patients. They analysed the effect of MMF on viremia, and measured *ex vivo* latently infected cells. The authors did not observe a significant decrease neither in HIV viremia nor in latent-infected cells, but the addition of MMF was not associated with detrimental effects [65].

In 2000, we started a pilot study in which HIV-infected patients ($n = 8$) receiving a combination of one nucleoside analogue and one PI (i.e. abacavir and amprenavir), with suppressed viraemia (i.e. plasma viraemia level <5 HIV-RNA copies/ml), were treated with MMF (500 mg twice a day for the first 4 weeks, followed by 1 g twice a day for 20 weeks) [66]. Data were compared with a group of eight HIV-infected patients, with the same clinical, immunological and virological characteristics, who received abacavir and amprenavir but not MMF.

In patients treated with MMF, we did not observe any decrease in total CD4 and CD8 T-cell percentage or count. Indeed, the mean cell values of CD4 T and CD8 T cells, at the initial period of the study were not significantly different from those at week 24, after treatment with MMF. Furthermore, there were no signs of haematological, liver and renal toxicity.

However, there was a statistically significant decrease in CD4 and CD8 dividing T cells ($Ki67^+CD4^+$ and $Ki67^+CD8^+$) in patients receiving MMF after 24 weeks of treatment, as opposed to patients without MMF, in whom the number and percentage of dividing CD4 and CD8 T cells remained stable. These results demonstrated that MMF can substantially influence the size of the pool of dividing CD4 and CD8 cells. To assess the virological effects due to the use of MMF, we evaluated the ability to isolate virus from purified CD4 T-cell populations at 8 and 20 weeks after the introduction of MMF. We observed a substantial reduction (up to 98%) in the titres of infectious units per million CD4 T cells in patients who received MMF, while in patients who continued HAART alone there was no significant change.

These data showed that the adjunction of MMF to HAART resulted in a reduction of proliferating CD4 and CD8 T cells and a decreased cellular viral load, from purified CD4 T cells. These results indicated that MPA may potentially inhibit HIV infection by a dual mechanism: (i) a direct antiviral mechanism exerted by depleting intra-cellular substrates for reverse transcriptase and (ii) an immunological mechanism through the reduction of activated CD4 T cells that favour HIV infection, as activated CD4 T lymphocytes are the primary target of HIV.

Based on these preliminary results, in a new prospective clinical study, we subsequently evaluated the impact of combining MMF (500 mg twice a day for 24 weeks) with HAART treatment interruption [67]. The rationale to use MMF during HAART interruption was to prevent immune activation induced by antiviral treatment interruption, therefore reducing the pool of activated and dividing CD4 T cells, which can favour virus replication.

In patients treated with MMF after HAART interruption ($n = 15$), we observed a reduced rebound of plasma viral load, compared with patients who did not receive MMF ($n = 6$). Furthermore, 80% of patients who received MMF, achieved a long-term control of virus replication (>1 year), compared with 66% in the control group after HAART interruption (NS). We concluded that HAART interruption along with MMF was safe, and it may prolong the control of virus replication. Our preliminary results showed that, similar to CsA, MMF (at doses comparable with those used in the transplant setting) can be used in HIV-infected patients safely without detrimental effects. MMF might even have beneficial effects in HIV patients by enhancing potency of some nucleotides analogues, or by being used during and after HAART interruption for chronically infected patients. More prospective studies with larger number of subjects are needed to confirm these results.

## Solid-organ transplantation in HIV-infected patients in the HAART era

### Liver transplantation

End-stage liver disease has become one of the most important causes of mortality and morbidity in HIV-infected patients, because these patients are often co-infected with HBV or HCV or both viruses.

A large multi-centre study of liver transplantation in HIV-infected patients reported the outcome of 24 subjects, who underwent liver transplantation between 1997 and 2001 at five different institutions [68]. The cause of end-stage liver diseases was HCV infection in 15 patients (62.5%), HBV infection in seven patients (29.2%) and fulminant hepatic failure in two patients (8.3%) in association with nevirapine-induced acute hepatic necrosis and acute hepatitis A infection.

Overall, patient survival was not different when compared with age and race-matched HIV-negative recipients. The cumulative patient survival at 12 months was 87.1% in HIV-infected patients compared with 86.6% in HIV-negative recipients, and at 24 months the survival was 72.8% in HIV-infected patients compared with 81.6% in HIV-negative recipients (NS).

The survival significantly decreased in HIV-infected transplant recipients, who developed intolerance to antiretroviral therapy after transplantation ($P = 0.044$), and antiretroviral intolerance was associated with HCV infec-

tion. Six patients (26.1%) experienced postoperative antiretroviral intolerance; of these patients, four (66.7%) died and all four had hepatitis C and developed antiretroviral intolerance, two in association with interferon and/or ribavirin therapy. However, patient survival in HCV-HIV co-infected recipients was not different from that of HCV positive–HIV negative recipients. Finally, patient survival was decreased in patients with low CD4 T-cell counts and high viral load after transplantation, reflecting the importance of a well controlled HIV infection.

These data reflect the difficulty of treating HCV recurrence in HIV-infected transplant recipients due to drug interactions and toxicities, complications of concomitant anti-HCV, HAART and immunosuppressive therapy.

Similarly, Norris *et al.* [69] described an increased mortality in HIV–HCV co-infected liver recipients due to severe HCV recurrence in the graft. They reported the outcome of 14 HIV-infected patients who received liver transplantation at King's College Hospital in London, between 1995 and 2003. In this cohort, the patients who underwent transplantation for HBV or alcohol-related cirrhosis had a long-term patient's survival, which was similar compared with non-HIV-infected recipients. In contrast, a lower patient's survival was observed in patients with HIV–HCV co-infection. At 2 years post-transplantation, five out of seven patients with HIV–HCV co-infection died. Therefore, according to their study, the survival rate of HIV–HCV co-infected recipients was lower than that of HCV-mono-infected recipients.

Recently, Vogel *et al.* reported a favourable outcome of four HIV–HCV co-infected liver recipients with a survival similar to that of non-HCV-infected recipients. In this report, HCV recurrence occurred in all four patients, however all were rapidly treated with pegylated interferon and ribavirin [70]. Anti-HCV treatment was initiated from 5 to 15 weeks after transplantation, with good virological responses. Intolerance to HAART, in patients receiving simultaneously IS and anti-HCV therapy was not observed.

Of note, HAART was initiated approximately 30 days after transplantation, and drugs known to have increased risk of mitochondrial toxicity and lactic acidosis (e.g. ddI or stavudine) were avoided.

These clinical studies highlight the importance of HIV–HCV co-infection in liver transplant recipients. However, an increased number of patients and longer prospective studies will be needed in order to define the best combinations of HAART, anti-HCV and IS therapy, as well as the best timing to start antiviral therapy and anti-HCV treatment.

While HCV infection is a major concern in liver transplantation, various clinical trials have shown that HBV infection is a treatable infection in HIV-negative organ recipients, as in HIV-positive recipients [69,71]. A major concern regarding HIV–HBV co-infection is the presence of HBV-lamivudine-resistant infection, because lamivudine is one of the major components of HAART and the most important anti-HBV drug. Lamivudine is a nucleoside analogue that has anti-HIV and anti-HBV activity. In HIV–HBV co-infected patients receiving prolonged treatment, it is known that the incidence of lamivudine-resistant HBV is approximately 50% after 2 years of therapy, and almost 100% after 4 years [72,73]. Newer drugs which are active against lamivudine-resitant HBV, such as adefovir, TFV or entecavir, will have to be used to treat these patients [74–76].

Recently, Terrault *et al.* [77] published the results of the San Francisco Transplant programme, in HIV–HBV co-infected patients. At the time of referral to waiting list, 67% of patients already met the criteria for lamivudine-resistant HBV infection and 48% of patients were on additional anti-HBV drugs such as adefovir, TFV or both. Finally, only four (11%) patients underwent transplantation. The mid-term outcome after transplantation was similar to non-HIV-infected recipients, with a median follow-up around 30 months. Furthermore, no episodes of opportunistic infections and acute rejection occurred. HIV-viral loads remained undetectable in all patients who were on continuous HAART. Despite a high prevalence of lamivudine-resistant HBV infection in these series, there was no evidence of HBV recurrence under antiviral therapy (lamivudine and/or adefovir or TFV) and hepatitis B immune globulin administration. These results indicate that the use of adefovir or TFV as alternative drugs can be effective to control HBV-resistant infection after liver transplantation. Interestingly, treatment with adefovir or TFV at the time of referral was the only factor identified as predictive of patient survival, with or without transplantation, demonstrating that patients on antiviral drugs with efficacy against lamivudine-resistant HBV have a higher survival rate. These data highlight the importance to monitor HBV-DNA regularly, in order to detect early virological break through and to initiate, soon, the most effective treatment.

### Kidney transplantation

Initial studies in the HAART era had shown no evidence of significant HIV progression after transplantation, and no adverse effect of HIV on allograft function. In particular, Stock *et al.* [71], in a pilot study, reported 10 HIV-positive kidney recipients with patient and graft survival at 1 year after transplantation of 100%. A high acute rejection rate of 50% was a major concern, indicating that HIV-infected patients maintained, however, the capacity to develop significant donor-specific immune responses

even in the presence of immunosuppressive drugs. This relatively high acute rejection rate might have been due to several factors, such as (i) lower usage of immunosuppressive agents due to drug interactions with HAART; or (ii) HIV viral rebound corresponding to HAART interruption for few days after transplantation, which induces an immune activation, thus possibly favouring rejection. Three of five patients with acute rejection required polyclonal anti-T-cell therapy, and only these patients developed a subsequent decrease in CD4 T cells resulting in severe but treatable infections. Despite significant drug interactions requiring modifications of doses of immunosuppressive drugs, HIV-RNA remained controlled in patients who continued their HAART. Overall, this preliminary experience was felt to be encouraging.

More recently, Kumar *et al.* [78] published the results of a prospective study where 40 HIV-infected patients with ESRD on dialysis underwent kidney transplantation [78]. Immunosuppressive therapy consisted of induction with basiliximab followed by triple immunosuppression with cyclosporin, sirolimus and steroids. After transplantation, HIV infection remained stable with CD4 T cells >400 cells/$mm^3$, undetectable HIV-RNA and no evidence of opportunistic infections up to 2 years post-transplantation. A 22% rate of acute rejection occurred in these HIV-infected patients. Acute rejection was treated with steroid boluses, and two patients with combined cell- and antibody-mediated rejection received also intravenous immune globulin and rituximab. In three recipients, the occurrence of acute rejection was due to subtherapeutical levels of cyclosporine which was caused by drug interactions with HAART, and in two patients, it was due to noncompliance. As in Stock's report [71], these data indicated that HIV-infected recipients on HAART are capable to mount an immune response against the allograft, inducing rejection. One- and two-year patient survival were 85% and 82%, and kidney allo-graft survival were 75% and 71% respectively. These results were also encouraging, i.e. demonstrating no progression of HIV infection under IS drugs.

Of note, patient and graft survival in HIV-infected patients was slightly lower when compared with non-HIV-infected patients, but similar to that of other high-risk populations receiving kidney transplantation.

Interestingly, Qiu *et al.* [29] reported the results of a clinical study where selected pairs of kidney allografts from the same donors ($n = 38$) were transplanted to either HIV-positive or HIV-negative patients. The 5-year graft survival in the HIV group was 76% compared with 65% in non-HIV group ($P = 0.21$), and 5-year patient survival was also similar in the two groups (respectively 91% in HIV group and 87% in non-HIV group, $P = 0.72$). Therefore, in this study, there were no statistically significant differences in graft and patient survival; however, HIV-infected patients underwent a slightly stricter patient selection. In fact, HIV-infected patients were younger and less often sensitized, i.e. they had a lower peak panel reactive antibodies before transplantation.

Carter *et al.* recently described the clinical experience of using thymoglobulin in HIV-infected kidney transplant recipients. They studied 20 HIV-infected patients who underwent kidney transplantation over a period of 4 years, and compared patients who received thymoglobulin with patients who did not receive this antilymphocyte preparation. The maintenance immunosuppressive regimen consisted of CNI steroids, MMF or sirolimus. Thymoglobulin was administered for delayed or slow graft function. After thymoglobulin administration, there was a profound decrease in CD4 T-cell count with a prolonged recovery, lasting up to 2 years, as described also in non-HIV-infected patients. Only one patient developed an opportunistic infection, but the other patients who received thymoglobulin also presented significant infections [79].

Finally, a NIH multi-center clinical trial is currently ongoing, and it plans to enrol HIV-infected patients for liver ($n = 125$) and kidney ($n = 150$) transplantation. The main objective of this important long-term study is to better evaluate the safety and efficacy of solid-organ transplantation in HIV-infected patients. The goals are also to provide information regarding HIV-specific risks after solid-organ transplantation as well as guidelines on the management of immunosuppressive drugs combined with HAART (http://www.hivtransplantation.com). The results of this trial will be awaited with great interest.

## Conclusions

With the advent of HAART, HIV infection has now become a chronic disease. Various end-stage organ failures have become common co-morbidities and significant causes of mortality in HIV-infected patients. In many centers, solid-organ transplantation has been proposed for these patients and HIV infection is not considered an absolute contraindication for transplantation.

Commonly used immunosuppressive drugs, such as CsA and MMF, can be used in HIV-infected patients safely without detrimental effects. These immunosuppressive drugs might even have beneficial effects for HIV patients; cyclosporin combined with HAART could be beneficial by increasing CD4 T-cell recovery for patients with primary HIV infection, and MMF might enhance the potency of some nucleotide analogues and it might contribute to the control of HIV replication after HAART interruption in chronically infected patients.

Recent reports of organ transplantation in HIV-infected patients are encouraging, with similar results of patient and graft survival as compared with non-HIV-infected patients. However, in certain countries, some centres still do not accept HIV-infected patients on their transplant waiting lists [80]. Nevertheless, in the majority of countries, solid-organ transplantation in HIV-infected patients has been initiated, but the series and clinical studies generally remain limited and the follow-up is relatively short.

Overall, it should be emphasized that organ transplantation in HIV patients remains a complex multidisciplinary intervention. A number of outstanding issues remain to be addressed. These include: (i) incidence and treatment of acute rejection, and consequences of anti-rejection therapy with steroid boluses or T-cell depleting agents; (ii) long-term patient and graft survival; (iii) type and timing of HAART in combination with immunosuppressive therapy; (iv) outcome of recurrent HCV infection and timing of anti-HCV therapy and (v) effect of newer immunosuppressive drugs, such as sirolimus/everolimus, or belatacept, on HIV infection.

In conclusion, the initial experience of solid-organ transplantation in HIV patients suggests that this intervention can probably be performed safely, but it requires careful management and expertise. Prospective studies in the near future will show how to improve the pre- and post-transplantation care of HIV patients.

## Authorship

DC – wrote the paper. GP – senior revision for HIV field. MP – senior revision for transplantation field.

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