

Transplantation[®]

OVERVIEW

REVIEW OF SOLID-ORGAN TRANSPLANTATION IN HIV-INFECTED PATIENTS

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Patients with HIV infection are at risk for end-stage organ disease. Before the highly active antiretroviral therapy (HAART) era, such patients were often not considered for transplantation because of poor prognosis. HIV-infected patients have experienced significant improvements in morbidity and mortality with HAART (1). Thus, increasing numbers of HIV-infected patients with end-stage organ disease are potential candidates for transplantation (2). Data on the safety and efficacy of solid-organ transplantation in people with HIV infection are limited, and the results are mixed. Before the HAART era, some transplant centers reported good outcomes (3–7); other reports have been less favorable (8, 9). Encouraging preliminary data are increasingly available in the HAART era (10–12).

WHY CONSIDER TRANSPLANTATION IN HIV-INFECTED PATIENTS NOW?

People with HIV infection are living longer and dying less often from AIDS-related complications but are experiencing morbidity and mortality secondary to organ failure. Although immunosuppression was once thought to be an absolute contraindication in the context of HIV infection, it is increasingly appreciated that immune activation is a prominent feature of HIV pathogenesis. Thus, immunosuppression may have beneficial effects in people with HIV infection through moderation of immune activation or reduction of HIV reservoirs. Specific immunosuppressant drugs also have antiviral properties or interact synergistically with certain antiretroviral agents (ARVs). Not only is there a need to consider transplantation in this population, there may even be benefits beyond those directly related to the new organ.

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Recent Advances in HIV Therapy and Improvements in Morbidity and Mortality

Clinical trials have demonstrated clear survival benefits associated with the use of protease inhibitor (PI)-containing or non-nucleoside reverse-transcriptase inhibitor (NNRTI)-containing regimens (HAART) (13). Epidemiologic data show decreased mortality, hospitalization rates, and opportunistic infection (OI) incidence associated with HAART (1, 14). There have been dramatic reductions in new AIDS-related OIs, most of which are now occurring in people with low CD4+ T-cell counts and those who are not receiving medical care. Epidemiologic and modeling data support the clinical trial efficacy data, suggesting that HAART has a significant impact on clinical outcome.

Prevalence and Natural History of End-Stage Renal Disease in HIV-Infected Patients

HIV-infected patients are at risk for end-stage renal disease (ESRD) caused by common and HIV-specific diseases, including HIV-associated nephropathy (HIVAN), immune complex glomerulonephropathy (GN), and hepatitis C (HCV)-associated cryoglobulinemic GN (15). HIVAN, a rapidly progressive disease of uncertain etiology, is the third leading causes of ESRD in African-American men. The prevalence ranges from 3.5 to 6.9%, and is 7 to 12% among African Americans, presumably because of human leukocyte antigen (HLA)-related disease susceptibility (16). Dialysis shortens survival in patients with HIV infection (17). The prognosis may be changing in the HAART era. Among a small group of patients, 4 of 7 patients not receiving HAART died at a mean of 13 months, while only 3 of 15 patients receiving HAART died at a mean of 28 months, suggesting HAART may increase survival in hemodialysis patients (18).

Prevalence and Natural History of End-Stage Liver Disease in HIV-Infected Patients

HIV-infected patients are at risk for HCV and hepatitis B (HBV) infection and the development of ESLD. The prevalence of HCV and HIV co-infection is approximately 23 to 33% (19). The prevalence of chronic HBV co-infection is approximately 9% (19). ESLD progression is accelerated in co-infected patients (20, 21) and may be complicated by ARV toxicity (22), immune-restoration-induced hepatitis (23), or the development of lamivudine-resistant HBV (24). ARV therapy can be associated with accelerated HCV disease progression thought to be secondary to immune reconstitution or

direct hepatotoxicity (23). ARV toxicity can cause fulminant hepatic failure with lactic acidosis and massive hepatic steatosis, although this is rare (25). Deaths caused by ESLD are of growing significance among patients with HIV infection. For example, Bica et al. (26) report that 50% of deaths in 1998 to 1999 were caused by ESLD compared with 11.5% in 1991 and 13.9% in 1996.

HIV Immune Pathogenesis

HIV infection is characterized by the progressive loss of CD4+ T cells and alterations in CD4+ T-cell function. Abnormal activation of CD8+ T cells may contribute to the loss of both CD4+ and CD8+ T cells through apoptosis, which may represent a major cause of infected and noninfected cell death in HIV infection. Many HIV-infected individuals lose CD4+ T-cell proliferative responses to recall antigens (e.g., influenza, tetanus), irradiated stimulator peripheral blood mononuclear cells (PBMCs) from healthy, unrelated (allogeneic) donors, or T-cell mitogens, such as phytohemagglutinin (27). HIV-infected transplant recipients may be at increased risk of accelerated CD4-infected T-cell depletion or increased CD4+ T-cell dysfunction, the development of opportunistic complications, or difficulty in controlling HIV replication. Conversely, immunosuppression might reverse the immunopathology associated with HIV disease.

Antiviral or Immune Modulating Effects of Cyclosporine and Mycophenolate Mofetil

Cyclosporine (CsA) may indirectly suppress viral replication by inhibiting interleukin (IL)-2-dependent proliferation of T cells. CsA prevents activation-induced CD4+ T-cell death in cells from HIV-infected subjects (28). In a retrospective review of HIV-infected transplant recipients, those using CsA progressed to AIDS at the same rate as nontransplanted HIV-infected patients, whereas those who did not receive CsA progressed at a faster rate (6). Although low-dose CsA in HIV-infected subjects did not significantly increase CD4+ T cells (29), a median increase in CD4+ T cells of 300 cells/mm³ was seen in subjects who received standard doses of CsA (30). Subjects who received PI-containing HAART and CsA (achieving trough levels seen in transplant recipients) immediately after diagnosis of acute HIV infection achieved a larger rise in CD4+ T cells than historical control subjects (31).

Mycophenolate mofetil (MMF) is being evaluated as a synergistic component of HAART. MMF forms mycophenolic acid (MPA), an inhibitor of inosine monophosphate dehydrogenase, an enzyme involved in the synthesis of deoxyguanosine triphosphate (dGTP). Reduction in intracellular dGTP concentrations may increase the ARV activity of abacavir (ABC), a guanosine analogue. In *in vitro* studies, MPA synergistically increases the antiviral effect of ABC (32) as well as didanosine (ddI) and tenofovir. Antagonism, likely caused by inhibition of thymidine kinase, was observed with MPA plus the thymidine analogues zidovudine (ZDV) and stavudine (d4T). Transplant recipients receiving MMF may experience synergistic antiviral effects or increased toxicity, if their HAART regimens contain ABC, ddI, or tenofovir. It may be prudent to limit the use of ZDV and D4T in this population when possible.

Effect of Immunosuppression on the HIV Viral Reservoir

Resting T lymphocytes are an important reservoir for HIV despite HAART (33). Immunosuppression may affect the reservoir of HIV-infected cells that persist during HAART by decreasing cell-associated HIV through either direct inhibition of viral replication, potentiation of HAART effects, or depletion of infected cells and reduction in the availability of permissive target cells by preventing T-cell activation. Alternatively, decreased immune control of HIV-expressing cells may result in enhanced viral reservoirs.

PUBLISHED SAFETY AND EFFICACY DATA IN THE PRE-HAART ERA

United Network for Organ Sharing (UNOS) policy does not consider HIV infection to be a contraindication for transplantation. HIV-infected patients have received transplants, although most were undiagnosed at the time of transplant or acquired HIV infection perioperatively. Although several initial papers reported poor outcomes following transplantation in HIV-infected recipients (8, 9), there have also been reports where there were no apparent adverse effects of HIV infection on allograft survival (3–7). Reports of two HIV-infected patients undergoing liver (5) or renal transplantation (7) demonstrated normal graft function for at least 8 years following transplant. The renal-transplant experience is the most promising, with the largest retrospective review demonstrating 6 of 11 renal allografts functioning at a mean follow-up of 31 months. Twenty-seven percent of the patients progressed to AIDS during this time, with no evidence of HIV-related opportunistic diseases in the remaining patients (4). The results were significantly worse in liver-transplant recipients who were found to be HIV-infected at the time of transplant (4). In this series, 5 of 7 died within 18 months of transplant, with 3 of the deaths being AIDS-related. More recent follow-up of liver-transplant recipients who acquired HIV through perioperative blood transfusion or infected organs demonstrated 5-year survival in 5 of 8 patients, and only 1 progressed to AIDS (6).

PRELIMINARY SAFETY AND EFFICACY DATA IN THE HAART ERA

We have described the preliminary outcomes of 53 kidney and liver transplant recipients in the HAART era (10). The analysis included prospective evaluation of patients participating in an on-going clinical trial and retrospective evaluation of patients transplanted at one of the centers participating in the trial before the trial was instituted at their site. Selection criteria included (1) no history of OI, (2) CD4+ T-cell counts of greater than 200 cells per milliliter for kidney recipients and greater than 100 cells per milliliter for liver recipients, and (3) HIV RNA less than 50 copies per milliliter (liver recipients could have detectable HIV RNA off ARVs if the study HIV clinician predicted full virologic suppression posttransplant). Forty-five subjects would have met the inclusion criteria for the clinical trial, and thus were considered “eligible.” Eight subjects did not meet the study criteria and thus were considered “ineligible.”

Among the eligible patients, 26 received kidney transplants and 19 received liver transplants. Median baseline CD4+ T-cells counts for the kidney recipients were 441 (200–1,054), and for the liver recipients were 280 (103–973). Me-

TABLE 1. Patient and graft-survival rates in HIV-infected and uninfected recipients

	UNOS cadaver kidney (%)	UNOS living kidney (%)	HIV and kidney (%)	UNOS liver (%)	HIV and liver (%)
Subject survival (n)					
UNOS 1 year	94.8	97.5	—	87.9	—
HIV + all	—	—	92 (N = 26)	—	79 (N = 19)
HIV + 1 year ^a	—	—	91 (N = 11)	—	92 (N = 12)
Graft survival (n)					
UNOS 1 year	89.4	94.5	—	87.9	—
HIV + all	—	—	85 (N = 26)	—	79 (N = 19)
HIV + 1 year ^a	—	—	71 (N = 11)	—	—

UNOS, United Network of Organ Sharing.

^a Limited to the subset of subjects who had at least 1 year of follow-up or who died in the first year, posttransplantation.

dian baseline HIV RNA in the liver recipients was less than 50 (<50–115,776). The median follow-up is 314 days (3–1,696). There were 6 deaths: 2 in kidney recipients (ischemic bowel and enterococcal sepsis in 1 patient and chronic rejection and *staphylococcal* sepsis 2 months after resumption of dialysis in the second patient) and 4 in liver recipients (recurrent HCV, rejection after PI was discontinued but immunosuppression dose was not adjusted, postoperative pancreatitis, and sinus thrombosis secondary to *rhizopus* infection 4.5 years posttransplant). Two AIDS-defining OIs occurred, cytomegalovirus (CMV) and candida esophagitis. Follow-up CD4+ T-cell counts remained stable: kidney recipients had a median of 436 (3–975), and liver recipients had a median of 218 (110–992). HIV RNA remained suppressed in most subjects. One liver recipient was retransplanted secondary to small-for-size graft failure following a living donation. Three kidney patients lost their grafts because of rejection (2) or thrombosis (1). Total rejection rates were 38% in kidney recipients and 21% in liver recipients. Subject and graft survival rates in this small sample were similar to 1-year survival rates in the UNOS database (Table 1).

In contrast, two of the eight ineligible subjects died of AIDS-associated complications including progressive multifocal leukoencephalopathy (PML) and disseminated mycobacterium avium complex (MAC). One of these subjects had advanced, undiagnosed AIDS at the time of transplant, and the other had incompletely evaluated altered mental status, another protocol exclusion. Those ineligible because of CD4+ T cell-count or HIV RNA criteria have done well, as have two subjects with a previous history of OI, who are both without recurrence at 6 and 15 months posttransplant. The current version of the clinical trial protocol has been modified to accept patients with specified OI histories.

SPECIAL CLINICAL CONCERNS

HBV and HBV Drug Resistance in the Context of HIV Antiviral Therapy. Transplant recipients co-infected with HIV and HBV may be at increased risk of recurrent or progressive HBV infection posttransplantation because of HIV-associated immune deficiencies or high rates of lamivudine (3TC)-resistant HBV. Without effective prophylactic therapy, 50% of HIV-negative liver transplant recipients experienced liver failure leading to graft loss within 5 years. With use of long-term HBIg prophylactic treatment, graft reinfection rates are reduced to approximately 20%. The natural history of HBV infection in kidney recipients is also accelerated.

Lamivudine, a cytosine analogue with activity against HIV

and HBV, is effective against HBIg-resistant HBV, reducing HBV reinfection rates in liver recipients to 20% in the first year; however, lamivudine resistance leads to treatment failure with longer duration of therapy. Combination HBIg and lamivudine is more effective, with success rates of 90 to 100% after 15 to 18 months follow-up. In HIV-negative patients, lamivudine resistance can develop within 6 months and is seen in 50% of patients after 3 years therapy. Lamivudine is a common component of HAART. Thus, HIV-infected patients on lamivudine for HIV treatment are at risk of having lamivudine-resistant HBV infection. Fortunately, lamivudine-associated mutants are sensitive to other nucleotide analogues, including adefovir dipivoxil and tenofovir (34, 35). There are no data on the effectiveness or safety of these agents in kidney recipients.

HCV Natural History in the Context of HIV Infection. Up to 240,000 people are co-infected with HCV and HIV, and HCV disease progresses more rapidly in HIV-infected patients (21). HCV disease progression is also accelerated in liver and kidney transplant recipients, but overall patient survival is improved. While nearly 100% of patients undergoing liver transplant for HCV develop recurrent infection, the spectrum of disease is variable. After 5 to 8 years, 8 to 30% of patients have bridging fibrosis or cirrhosis. A minority of transplant recipients with HCV develop cholestasis and rapidly progressive hepatitis, a syndrome called fibrosing cholestatic hepatitis (FCH). Immunosuppression related to HIV infection may result in accelerated posttransplant HCV-disease progression. Preliminary data available in HIV-HCV co-infected patients are inconsistent, with excellent outcomes reported from the University of Pittsburgh (12) and poor outcomes reported from King's College (11). Given the prevalence of co-infection, the accelerated natural history of HCV infection in HIV-infected patients and the inconsistent initial experience with transplantation in this population, this is an area of both special urgency and heightened concern.

Human Herpesviruses (CMV, HHV-6, HHV-8, EBV) and the Intersection of Clinical Disease Manifestations in HIV Infection and Transplantation. Opportunistic infections with herpesviruses (CMV, Epstein-Barr virus [EBV], human herpes virus [HHV]-6, and HHV-8) are a significant cause of morbidity and mortality in both organ transplant recipients and HIV-infected patients because of suppression of host antiherpesvirus T-cell immunity. The important contribution of host immunity to the control of viral infection is illustrated by the resolution of Kaposi's sarcoma (KS) in HIV-negative transplant recipients when immunosuppression is reduced.

Similarly, control of KS and CMV-associated diseases is improved with ARV-induced immune reconstitution. Therefore, posttransplant immunosuppression may lead to reactivation and increased replication of these viral pathogens.

Among the herpesviruses, CMV causes the most serious diseases in both HIV-infected patients and transplant recipients. Retinitis is the most common CMV disease manifestation in HIV-infected patients, and CMV hepatitis, gastroenteritis, and pneumonia are common in transplant recipients. EBV is a cause of posttransplantation lymphoproliferative disease, and it is associated with central-nervous-system lymphomas in HIV-infected patients. While HHV-6 has not been linked to disease in HIV-infected persons, it is associated with pneumonitis and graft rejection in transplant recipients (36), and HHV-6 reactivation increases the risk of posttransplant CMV disease. Virtually all HIV-infected patients are HHV-6 seropositive. HHV-8 causes KS. Eight to 28% of HHV-8-infected transplant recipients develop KS (37). HHV-8 infection may also result in other posttransplant complications, including fever, rash, hepatitis, neutropenia, and thrombocytopenia. Although less than 10% of the general population in the United States is HHV-8 seropositive, 50 to 60% of HIV-infected men who have sex with men (MSM) are HHV-8 seropositive (38), as are an estimated 15% of HIV-infected women (39).

Human Papilloma Virus and the Intersection of Clinical Disease Manifestations in HIV Infection and Transplantation. Transplant recipients are at 5 to 100-fold higher risk for human papilloma virus (HPV)-associated cancers (40). Ninety-three percent of all HIV-infected MSM and 75% of HIV-infected women have anal HPV infection. Anal intraepithelial neoplasia (AIN), the putative precursor lesions to anal cancer, is also very common among both HIV-infected men and women (41, 42). HAART does not improve the course of AIN (43), and the incidence of anal and cervical cancer has not declined in the HAART era. HIV-infected men are at 37-fold higher risk of anal cancer than the general population, and HIV-infected women are at 8-fold higher risk (44). Posttransplant, the course of AIN may be accelerated because of the combined risk associated with HIV infection and with immunosuppression.

Impact of HIV Infection on the Alloimmune Response and Allograft Rejection. Perturbations of the immune system associated with HIV infection may influence the immune response to allografts. HIV infection can cause impaired responses to allogeneic stimulation (27), suggesting that it may be possible to reduce immunosuppressive medications. However, preliminary experience demonstrates that HIV-positive transplant recipients can reject their grafts (10). Alterations in T-cell repertoire have been observed in HIV-infected individuals as well as kidney-transplant recipients (45, 46). Although generation of naive T cells contributes to the increased CD4+ T-cell counts, the majority of the T cells initially repopulating the periphery following HAART initiation are derived from memory cells. If expanded T cells have cross-reactivity with alloantigens on the graft, these cells may cause graft rejection.

Pharmacokinetic Interactions Between Immunosuppressive Agents and ARVs. Many of the immunosuppressive drugs (CsA, tacrolimus, and sirolimus), as well as the PIs and NNRTIs, are hepatically metabolized by the cytochrome P-450 enzymatic system. P-glycoprotein (P-gp) is a drug-

efflux pump expressed on the apical surfaces of many epithelial cells. P-gp expression and function and cytochrome P450A function can be affected by both sets of drugs. Drug interactions may require dosing modifications to maintain appropriate drug levels; over or under dosing carries the risk of toxicity, transplant rejection, or HIV rebound. Our preliminary experience shows that giving a PI with another P-gp inhibitor can markedly change the exposure of one or both drugs (47). For example, adding a calcineurin inhibitor to a PI-containing regimen markedly increases the calcineurin inhibitor levels. In contrast, NNRTI use has minimal effect on calcineurin inhibitor levels. The impact of the immunosuppressant on ARV drug levels is under investigation.

CONCLUSIONS

The care of transplant recipients with HIV infection requires a well coordinated, multidisciplinary team of care providers with expertise in transplant and HIV medicine and pharmacology. Ongoing and planned clinical trials will be instrumental in defining clinical practice guidelines in this complex area. In the meantime, there is no ethical justification for withholding transplantation from this population (2), and the early experience in the HAART era is very encouraging.

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REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; 338(13): 853.
2. Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. *N Engl J Med* 2002; 347(4): 284.
3. Tzakis AG, Cooper MH, Dummer JS, et al. Transplantation in HIV+ patients. *Transplantation* 1990; 49(2): 354.
4. Schwarz A, Offermann G, Keller F, et al. The effect of cyclosporine on the progression of human immunodeficiency virus type 1 infection transmitted by transplantation: data on four cases and review of the literature. *Transplantation* 1993; 55(1): 95.
5. Jacobson SK, Calne RY, Wreghitt TG. Outcome of HIV infection in transplant patient on cyclosporin [letter]. *Lancet* 1991; 337(8744): 794.
6. Erice A, Rhame FS, Heussner RC, et al. Human immunodeficiency virus infection in patients with solid-organ transplants: report of five cases and review. *Rev Infect Dis* 1991; 13 (4): 537.
7. Ahuja TS, Zingman B, Glicklich D. Long-term survival in an HIV-infected renal transplant recipient. *Am J Nephrol* 1997; 17(5): 480.
8. Ragni MV, Bontempo FA, Lewis JH. Organ transplantation in HIV-positive patients with hemophilia [letter]. *N Engl J Med* 1990; 322(26): 1886.
9. Poli F, Scalapogna M, Pizzi C, et al. HIV infection in cadaveric renal allograft recipients in the North Italy Transplant Program. *Transplantation* 1989; 47(4): 724.
10. Roland MC, Ragni L, Rohal M, et al. Solid organ transplantation in HIV-infected recipients: forty-seven cases in the HAART-era. Presented at the XIV International AIDS Conference, Barcelona, Spain, July 7-12, 2002.
11. Prachalias AA, Pozniak A, Taylor C, et al. Liver transplantation in adults coinfecting with HIV. *Transplantation* 2001; 72(10): 1684.
12. de Vera ME, Eghtesad B, Jain A, et al. Liver transplantation in patients co-infected with HIV and hepatitis C. Presented at the American Transplant Congress 2002, Washington, DC, April 25-May 1, 2002.
13. Department of Health and Human Services, Henry J. Kaiser Family

- Foundation. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. *MMWR Recomm Rep* 1998; 47 (RR-5): 43.
14. Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *Jama* 1998; 280(17): 1497.
 15. Rao TK, Friedman EA, Nicastrì AD. The types of renal disease in the acquired immunodeficiency syndrome. *N Engl J Med* 1987; 316(17): 1062.
 16. Shahinian V, Rajaraman S, Borucki M, et al. Prevalence of HIV-associated nephropathy in autopsies of HIV-infected patients. *Am J Kidney Dis* 2000; 35(5): 884.
 17. Perinbasekar S, Brod-Miller C, Pal S, et al. Predictors of survival in HIV-infected patients on hemodialysis. *Am J Nephrol* 1996; 16(4): 280.
 18. Ahuja TS, Borucki M, Grady J. Highly active antiretroviral therapy improves survival of HIV-infected hemodialysis patients. *Am J Kidney Dis* 2000; 36(3): 574.
 19. Ockenga J, Tillmann HL, Trautwein C, et al. Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *J Hepatol* 1997; 27(1): 18.
 20. Colin JF, Cazals-Hatem D, Lioriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999; 29(4): 1306.
 21. Lesens O, Deschenes M, Steben M, et al. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. *J Infect Dis* 1999; 179(5): 1254.
 22. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *Jama* 2000; 283(1): 74.
 23. Puoti M, Gargiulo F, Roldan EQ, et al. Liver damage and kinetics of hepatitis C virus and human immunodeficiency virus replication during the early phases of combination antiretroviral treatment. *J Infect Dis* 2000; 181(6): 2033.
 24. Bessesen M, Ives D, Condeay L, et al. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis* 1999; 28(5): 1032.
 25. Carr A, Morey A, Mallon P, et al. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia. *Lancet* 2001; 357(9266): 1412.
 26. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis* 2001; 32(3): 492.
 27. Shearer GM, Clerici M. In vitro analysis of cell-mediated immunity: clinical relevance. *Clin Chem* 1994; 40 (11 Pt 2): 2162.
 28. Groux H, Torpier G, Monte D, et al. Activation-induced death by apoptosis in CD4+ T cells from human immunodeficiency virus-infected asymptomatic individuals. *J Exp Med* 1992; 175(2): 331.
 29. Calabrese LH, Lederman MM, Spritzler J, et al. Placebo-controlled trial of cyclosporin-A in HIV-1 disease: implications for solid organ transplantation. *J Acquir Immune Defic Syndr* 2002; 29(4): 356.
 30. Andrieu JM, Even P, Venet A, et al. Effects of cyclosporin on T-cell subsets in human immunodeficiency virus disease. *Clinical Immunology and Immunopathology* 1988; 47(2): 181.
 31. Rizzardì GP, Harari A, Capiluppi B, et al. Treatment of primary HIV-1 infection with cyclosporin A coupled with highly active antiretroviral therapy. *J Clin Invest* 2002; 109(5): 681.
 32. Margolis D, Heredia A, Gaywee J, et al. Abacavir and mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase, have profound and synergistic anti-HIV activity. *J Acquir Immune Defic Syndr* 1999; 21(5): 362.
 33. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med* 1999; 5(5): 512.
 34. Perrillo R, Schiff E, Yoshida E, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. *Hepatology* 2000; 32(1): 129.
 35. Ying C, De Clercq E, Nicholson W, et al. Inhibition of the replication of the DNA polymerase M550V mutation variant of human hepatitis B virus by adefovir, tenofovir, L-FMAU, DAPD, penciclovir and lobucavir. *J Viral Hepat* 2000; 7(2): 161.
 36. Kosuge H. HHV-6, 7 and their related diseases. *J Dermatol Sci* 2000; 22(3): 205.
 37. Cattani P, Nanni G, Graffeo R, et al. Pretransplantation human herpes virus 8 seropositivity as a risk factor for Kaposi's sarcoma in kidney transplant recipients. *Transplantation Proceedings* 2000; 32(3): 526.
 38. Martin JN, Ganem DE, Osmond DH, et al. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 1998; 338(14): 948.
 39. Greenblatt RM, Jacobson LP, Levine AM, et al. Human herpesvirus 8 infection and Kaposi's sarcoma among human immunodeficiency virus-infected and -uninfected women. *J Infect Dis* 2001; 183(7): 1130.
 40. Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients. *Clin Transpl* 1990: 53.
 41. Palefsky JM, Holly EA, Ralston ML, et al. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *Aids* 1998; 12(5): 495.
 42. Holly EA, Ralston ML, Darragh TM, et al. Prevalence and risk factors for anal squamous intraepithelial lesions in women. *J Natl Cancer Inst* 2001; 93(11): 843.
 43. Palefsky J, Holly E, Ralston M, et al. The effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. *J Acquir Immune Defic Syndr* 2001; 27(5): 422.
 44. Frisch M, Biggar RJ, Engels EA, et al. Association of cancer with AIDS-related immunosuppression in adults. *Jama* 2001; 285(13): 1736.
 45. Kolopp-Sarda MN, Renoult E, Gregoire MJ, et al. Increased usage of TCR V-beta8 in kidney transplant recipients with aberrant immune reconstitution and clinical complications. *Transplantation* 1999; 67(11): 1441.
 46. Giovannetti A, Pierdominici M, Mazzetta F, et al. T cell responses to highly active antiretroviral therapy defined by chemokine receptors expression, cytokine production, T cell receptor repertoire and anti-HIV T-lymphocyte activity. *Clin Exp Immunol* 2001; 124(1): 21.
 47. Baluom M FL, Carlson L, Roland ME, et al. A one year evaluation of the interactions between antiviral immunosuppressant medication in HIV+ kidney and liver transplant patients. Presented at the AAPS Annual Meeting and Exposition, Toronto, Ontario, Canada, November 10-14, 2002.