Renal transplantation in patients with HIV/AIDS

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Renal Transplantation in Patients with HIV/AIDS

GRADUATION PAPER

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Summary

The human immunodeficiency virus (HIV)-infected patient is more prone to developing both acute and chronic renal failure than the general population. Renal disease specific to the HIV-infected population include HIV-associated nephropathy (HIVAN), mostly prevalent in the black population, and HIV immune complex kidney disease (HIVICK), which is more common in the white population. Some immune complex diseases of the kidney are thought, in the majority of cases, to originate from a co-infection with hepatitis C virus (HCV). As the life expectancy of this population is getting longer they are more likely to suffer from end organ damage due to age related diseases such as hypertension (HTN) and diabetes mellitus (DM). The kidney function can be monitored by estimated glomerular filtration rate (eGFR), albumin/creatinine ratio (ACR) and protein/creatinine ratio (PCR). Using ACR and PCR enables estimation of the renal function even in dilute urine and does not need sensitive lab machines, necessary for detecting tubular proteins in urine, that are not available at many hospitals. Treatment of established kidney disease is by managing modifiable factors, such as HTN, body weight and drug regimen as far as possible. Renal replacement therapy is indicated as for other patient groups with decreased renal function. If the patient fulfil certain criteria they are eligible for a renal transplant. Social stigma and lack of knowledge has led fewer HIV-infected patients to want transplantation. Among the HIV-specific criteria for transplantation include that the patient has to be well regulated with combined ART (cART) for at least six months and without a history of opportunistic infections. Immunosuppressive (IS) therapy was for a long time thought to enable the virus to freely replicate and hasten the progression to AIDS and death. Studies have later shown that by suppressing the immune system one is preventing activation of CD4+ T cells and, because the HIV-virus infect activated cells, they also protect new T-cells from being infected. IS may thus, on the contrary, even be beneficial in these patients. The drug interactions between IS and ART are many and complex and it is beneficial with multidisciplinary teams, including a infectologist and nephrologist, to choose the optimal therapy. Blood levels of the drugs should be checked with regular intervals to ensure therapeutic levels and prevent nephrotoxicity or rejection. The outcome after transplantation is continuing to improve. The frequency of rejection episodes is higher in this population, but the graft and patient survival is similar to the general population. Meta-analyses have concluded that renal transplantation should be offered to patients who fulfill the criteria, although the strength of evidence is very low due to small study samples.

Key words: chronic kidney disease, HIV, transplantation.

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Acronyms

ART	Anti-retroviral therapy
cART	Combined ART
HAART	Highly active ART
IS	Immunosuppressant
PI	Protease inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
EFV	Efavirenz
NVP	Nevirapine
CsA	Cyclosporine A
TAC	Tacrolimus
HTN	Hypertension
DM	Diabetes mellitus
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
RRT	Renal replacement therapy
ARF	Acute renal failure
AKI	Acute kidney injury
CKD	Chronic kidney disease
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
NSAID	Non-steroidal anti-inflammatory drug
ACE inhibitor	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
HCV	Hepatitis C virus
HBV	Hepatitis B virus
PCR	Protein-Creatinine ratio
ACR	Albumin-Creatinine ratio
CG	Cockroft-Gault
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
MDRD	Modification of Diet in Renal Disease
LDKT	Living donor kidney transplantation
GALT	Gut associated lymphoid tissue
PRA	Panel reactive antibodies
NSTEMI	Non-ST elevation myocardial infarction
CNI	Calcineurin inhibitors
BMI	Body mass index
HSCT	Hematopoietic stem cell transplantation
HiB	Hemophilus influenza type B
CMV	Cytomegalovirus
PCP	Pneumocystis carinii pneumonia
NODAT	New onset of diabetes mellitus after transplantation
RCT	Randomized control trial
DGF	Delayed graft function
AUC	Area under the curve
STI	Sexually transmitted infection
UTI	Urinary tract infection
TMP-SMX	Trimethoprim-Sulfamethoxazole

Summary of drugs

Immunosuppressants

Calcineurin-inhibitors / IL-2 inhibitors

- Cyclosporine A
- Tacrolimus

Anti-metabolites

- Mycophenolate mofetil

m-TORs

- Sirolimus
- Everolimus

Anti-lymphocyte antobodies

- Thymoglobulin
- Anti-thymocyte globulin

Anti-CD25 monoclonal anti-lymphocyte antibody

- Basiliximab

Corticosteroids

- Methylprednisolone
- Prednisone

Antiretrovirals

Nucleoside reverse transcriptase (NRTIs)

- Abacavir

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Zidovudine
- Didanosine
- Efavirenz
- Nevirapine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir

Protease inhibitors (Pis)

- Indinavir
- Saquinavir
- Nelfinavir
- Ritonavir
- Fosamprenavir
- Lopinavir
- Atazanavir
- Tipranavir
- Darunavir

CCR 5 Co-receptor agonist

- Maraviroc

Fusion inhibitors

- Enfurvitide

Integrase inhibitors

- Raltegravir
- Dolutegravir
- Elvitegravir/Cobicitat

Co-formulated agents

- Combivir
  Lamivudine/Zidovudine
- Epzicome
  Abacavir/Lamivudine
- Trizivir
  Abacavir/Lamivudine/Zidovudine
- Atripla
  Efavirenz/Emtricitabine/Tenofovir
- Complira
  Emtricitabine/Rilpivirine/Tenofovir
- Stribild
  Elvitegravir/Cobicistat/Emtricitabine/ Tenofovir

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Introduction

The life span of a person infected with human immunodeficiency virus (HIV) has significantly improved since its appearance in the 1980's, and is now approaching that of the general population. This has consequently led to a higher prevalence of age related diseases that also affect kidney function, such as hypertension (HTN) and diabetes mellitus (DM). Apart from those conditions there are other factors more specific to the HIV-infected

population with nephrotoxicity due to antiretroviral drugs, HIV-associated nephropathy (HIVAN) and immune complex-mediated glomerulonephritis to mention some. Although the prevalence of HIV-infected patients requiring renal replacement therapy (RRT) in Europe is fairly low, it is increasing due to the aforementioned factors. Patients infected with HIV were for a long time not considered eligible for renal transplantation due to fear that the subsequent immunosuppressive therapy would increase viral load and hasten the progression of their infection. With the introduction of highly active anti-retroviral therapy (HAART), increasing knowledge about the pathophysiology of the disease and novel immunosuppressive medication in the 1990's, transplantation results were not much worse in comparison with the HIV-negative population. One obstacle that remains still is the higher frequency of delayed graft function and acute rejection in this patient group, but constant development in knowledge and understanding of the immunosuppressive agents keep improving the outcome in this population. Renal transplantation is a treatment option that should be considered after individual evaluation of each patient with HIV and end-stage renal disease (ESRD).

History of HIV/AIDS

On June 5th 1981, the Center for Disease Control in the U.S. published a Morbidity and Mortality Weekly Report describing the finding of infections attributed to a non-functioning immune system in five apparently healthy young gay men in Los Angeles. Shortly thereafter more case series followed. In the next year, more than tens of thousands were appreciated to be infected, and the term Acquired Immune Deficiency Syndrome was coined on September 24th 1982. The definition was then "a disease at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease.", but it was not until 1986 that the virus was named *Human Immunodeficiency Virus*, HIV. One year later, and six years after the first report of acquired immuno deficiency syndrome (AIDS), Food and Drug Administration (FDA) approves the first antiretroviral drug: Zidovudine. By 1994, AIDS had become the leading cause of death in all Americans in the age between 25 and 44 years. In 1995, the first Protease Inhibitor was FDA approved and we enter the era of HAART. The following year, AIDS was no longer the leading cause of death in the young and previously healthy, except in the African American population, and the world is for the first time feeling careful optimism. In 1997, 47% less patients died of AIDS or AIDS-related diseases than the previous year, which was mostly attributed to the introduction of HAART. Combination pills are starting to be produced to increase

compliance, the first *Non-Nucleoside Reverse Transcriptase*, NNRT, was approved, but resistance starts to become a problem.

As the HIV/AIDS epidemic is starting to get under control in the U.S., Canada and Europe, reports on major spread on the African continent are appearing and it is the number one killer in their whole population. The UNAIDS (the joint United Nations programme on AIDS) reports in 2002 that the average life expectancy has decreased from 62 to 47 years solely due to HIV/AIDS.[1]

Etiology of impaired kidney function in patients with HIV/AIDS

Kidney disease can be classified as acute or chronic: glomerular, vascular or tubulointerstitial. HIV-infected patients may develop nephropathies due to many reasons such as a secondary cause of the virus itself, the antiretroviral therapy and/or some co-infection with e.g. hepatitis C.

Table 1. Kidney disease associated with human immunodeficiency virus (HIV) infection. Shown are diseases that are associated with HIV infection or its treatment. *Certain glomerular diseases are commonly associated with other viral infections or may occur on an idiopathic basis; a true association with HIV disease is uncertain or doubtful. Collapsing glomerulopathy is notable for glomerular, tubular and interstitial disease but is classified under glomerular disease for simplicity. According to Johnson RJ, Feehally J, Floege J (2015), p.683

Kidney Diseases Associated with HIV Infection

	Entity	Frequency	Associations
Glomerular	Collapsing glomerulopathy	Common	African descent; particularly advanced HIV disease
	Immune complex glomerulonephritis	Common	European, Asian descent, and black Africans in Africa
	Thrombotic microangiopathy	Uncommon	
	Membranoproliferative glomerulonephritis, with or without cryoglobulin-associated vasculitis	Rare*	Hepatitis C; enfuvirtide
	Membranous nephropathy	Rare*	Hepatitis B
	Fibrillary and immunotactoid glomerulopathies	Rare*	
	Amyloid nephropathy (AA type)	Rare*	
	Minimal change nephropathy	Rare*	Nonsteroidal anti-inflammatory medication
Tubular	Acute kidney injury	Moderately common	Aminoglycosides, cidofovir foscarnet
	Proximal tubule injury (Fanconi syndrome)	Moderately common	Tenofovir, adefovir, cidofovir, didanosine
	Diabetes insipidus	Uncommon	Amphotericin, tenofovir, didanosine, abacavir
	Chronic tubular injury	Moderately common	Amphotericin, cidofovir, adefovir, tenofovir
	Crystal nephropathy	Uncommon	Indinavir, atazanavir; sulfadiazine, ciprofloxacin, intravenous acyclovir
Interstitial	Interstitial nephritis	Uncommon	Allergy to β-lactam, sulfa, ciprofloxacin, rifampin, proton pump inhibitor, allopurinol, phenytoin; also causes of crystal nephropathy listed above
			BK virus; generally advanced disease
			Immune reconstitution inflammatory syndrome; generally advanced disease; following initiation of ART

Acute renal failure

Acute renal failure (ARF) is defined differently across studies, but a consistent feature is a drop glomerular filtration rate (GFR) with subsequent sequelae such as electrolyte derangements, encephalopathy and volume overload that may have a fatal outcome.[2] In a study where ARF was investigated in HIV positive patients it was found that 6 % of their inpatients had ARF with a mortality rate of 27 %. The incidence in the outpatient group the incidence was up to 10 % with approximately one third secondary to drugs[3] but HIV infection by itself had also been associated with ARF[4]. One study found that more than half of the episodes of ARF were attributed to infection with 76% of these being an AIDS-defining illness.[5]

Chronic kidney disease

Chronic kidney disease (CKD) is defined as a decrease in GFR <60ml/min/1.73m² or renal damage (proteinuria, albuminuria, histological abnormalities in the biopsy, the urinary sediment or imaging techniques) that persists for more than three months.[6] Risk factors for CKD include HTN, DM, advanced age, a low CD4 nadir, a high HIV viral load and the use of potentially nephrotoxic medication.[7-11] The prevalence differs with ethnicity and is higher in areas with less access to treatment.[12] Kidney Disease Improving Global Outcomes (KDIGO) proposed a new classification for prognosis of CKD in 2012 including GFR and albuminuria; the patients are divided into six categories depending on the urinary albumin/creatinine ratio (ACR) and eGFR. The risk outcome events include overall mortality, cardiovascular mortality, renal failure treated with dialysis or transplantation, ARF and progression of renal disease.[13, 14] Approximately 7.1 % of HIV-infected patients have an estimated GFR (eGFR)[12] <60ml/min/1.73m^2 and the prevalence of albuminuria have been measured in several studies to between 11 % and 15.5 %.[15]

Antiretroviral drug-induced nephrotoxicity

Nephrotoxicity as a consequence of antiretroviral therapy is uncommon today, although it is suspected that it will increase along with the aging of the population. The risk of having a decrease in eGFR is mostly associated with Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), with Tenofovir (TDF) in particular, and Protease Inhibitors (PIs), such as Atazanavir (ATV) and Lopinavir (LPV). The higher risk of renal toxicity with the above mentioned drugs is controversial and may be due to drug interactions in between the antiretroviral drugs. The toxicity causes functional abnormalities of the tubular proteins,

mainly in the proximal part, causing a clinical picture similar to Fanconi syndrome. This, in full, include phosphaturia, glucosuria with normoglycemia, renal tubular acidosis with normal anion gap, aminoaciduria, tubular proteinuria and medium-long-term renal failure.[16-22] The damage caused by TDF toxicity is usually reversible, but may not be complete.[23] One center reported that the administration of TDF each year resulted in a 34 % increased risk of developing proteinuria, 11 % increased risk of rapid decline and a 33 % increased risk of CKD[24]. Several studies have shown specific toxicity of TDF when used in combination with certain drugs, for example Didanosine. It has been suggested that it might be of greater benefit to regulate the combination of drugs than to exclude TDF, which has demonstrated a positive effect in several randomized control trials. This strategy requires a regular monitoring of kidney function.[25]

Table 2. Renal toxicity of antiretroviral therapy. Effects of toxicity and their management. According to Johnson RJ, Feehally J, Floege J (2015), p. 685

Renal Toxicity of Antiviral Therapy			
Antiretroviral Class	**Antiretroviral Therapy**	**Renal Effect**	**Clinical Recommendations**
Protease inhibitors	Indinavir	Nephrolithiasis, crystalluria, dysuria, papillary necrosis, acute kidney injury, interstitial nephritis	Daily fluid intake of >2 l/day
		Ritonavir and lopinavir may increase toxicity of indinavir	
	Ritonavir	Reversible AKI (usually in combination with nephrotoxic drugs)	
	Saquinavir, nelfinavir	Renal calculi (rare)	Increased fluid intake
Reverse transcriptase inhibitors	Tenofovir, abacavir	Renal tubular damage: proximal tubular dysfunction, Fanconi syndrome, nephrogenic diabetes insipidus, acute tubular necrosis, AKI	Patients taking tenofovir should be monitored for signs of tubular dysfunction (elevated serum creatinine, hypophosphatemia, low serum uric acid, acidosis glycosuria, proteinuria)
	Didanosine, lamivudine, stavudine	Isolated case reports of tubular dysfunction	
Other	Cidofovir, adefovir	Renal tubular damage, proximal tubular dysfunction (cidofovir)	

Non-antiretroviral drug-induced nephrotoxicity

HIV infected persons might need other drugs during the course of life that are nephrotoxic. This might be due to co-morbidities, opportunistic infections or non-HIV-related conditions. The groups of drugs most commonly implicated are certain Antiobiotics and Antivirals, Non-steroidal Anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE)-inhibitors/angiotensin receptor blockers (ARBs) and iodinated contrasts. These drugs, if possible, should be avoided or dose adjusted according to current kidney function.[2]

Glomerular and vascular nephropathies

The spectrum of glomerular pathologies is wide and dependent on race, co-infection with Hepatitis C (HCV) virus or any other co-infection, and the control of their HIV. In previous years HIV associated nephropathy (HIVAN) was more prevalent, whereas today older age and cardiovascular causes are more prominent.[26]

HIV-associated nephropathy

HIV-associated nephropathy (HIVAN) is the best defined type of nephropathy in this population. It is characterized by a focal and segmental collapsing glomerulosclerosis on histology. Clinically the main manifestation is proteinuria, which frequently reaches over 3.5g/24h, although the clinical impact seems to be less severe than patients with other causes of nephrotic syndrome.[27] It is more prevalent in the Black than the Caucasian patients with a ratio of 12:1.[28, 29] The higher prevalence of HIVAN in the black population has been associated with a variant in APOL1 gene. This gene is protecting against trypanosomiasis, but has also been shown to increase the risk of developing kidney disease.[30, 31] The outcome of HIVAN without ART is poor, often with progression to renal failure requiring dialysis within one year of diagnosis and a high mortality rate.[32] Since the introduction of combined ART (cART), the clinical course has improved.[33] Several observational studies have shown a reduced risk of developing HIVAN and improved prognosis with ART, but until today no controlled clinical trials have been performed.[33-37] Treatments including ACE-inhibitors or ARBs may delay progression to renal failure. They are indicated when HIVAN is associated with hypertension or proteinuria.[38] Some studies showed the benefit of steroid therapy in slowing down the progression to renal failure, but this may in addition to the known side effects be particularly problematic in patients with impaired immunity[39] and is not used routinely[2], but only when it is resistant to therapy with ART and ACE-inhibitor/ARB.[39]

HIV-associated immune complex kidney disease (HIVICK)

Impaired renal function due to deposits of immune complexes is more common in the HIV-infected persons than in the general population. HIVICK is a histological diagnosis that can have different etiologies with the HIV- infection itself being a cause, post-infectious glomerulonephritis[40] or a co-infection with HBV- or HCV-infection. Histological appearance is varied, but the clinical manifestations are usually very apparent with macroscopic hematuria, edema, ARF and severe hypertension.[2] IgA deposits are thought to be a direct consequence of the HIV infection.[41] Sometimes other more discrete manifestations occur

including cryoglobulinemia with evidence of purpura, digestive symptoms and alveolar hemorrhage. Some of these lesions show deposits of IgG and IgM complexes usually associated with HCV-infection, and it has been suggested that this is in fact induced by the HCV infection with the HIV-infection having a marginal role. [42-44] Data on the natural history of HIVICK, treatment options and response to cART are limited [45-49], and it is not known whether or not it can be modified through therapies used in HIV-negative patients such as steroids, immunosuppressants and calcineurin inhibitors. In the cases where there is a HCV co-infection studies have shown improvement of renal function with effective anti-hepatitis therapy including Ribavirin and alpha-interferon. [44, 50]

Diabetic nephropathy and hypertensive nephropathy

The metabolic consequences of antiretroviral therapy include dyslipidemia, body fat changes, insulin resistance and DM. These features are common in the general population as well and tend to increase with age. In the general population the cause of ESRD due to DM and HTN today is as high as 70 %.[51] With the improvement of ART and longer life expectancy it is likely that these features will become more evident in the HIV- infected population as well. Some series of kidney biopsies have shown diabetic nephropathy in 6 % and hypertensive nephropathy in 4 %. [52, 53] Albuminuria is an independent risk factor for both cardiovascular disease and renal disease[54], and because it has a high prevalence in the HIV-infected population[15], the incidence in renal disease can be expected to increase in the future.[2]

Monitoring kidney function

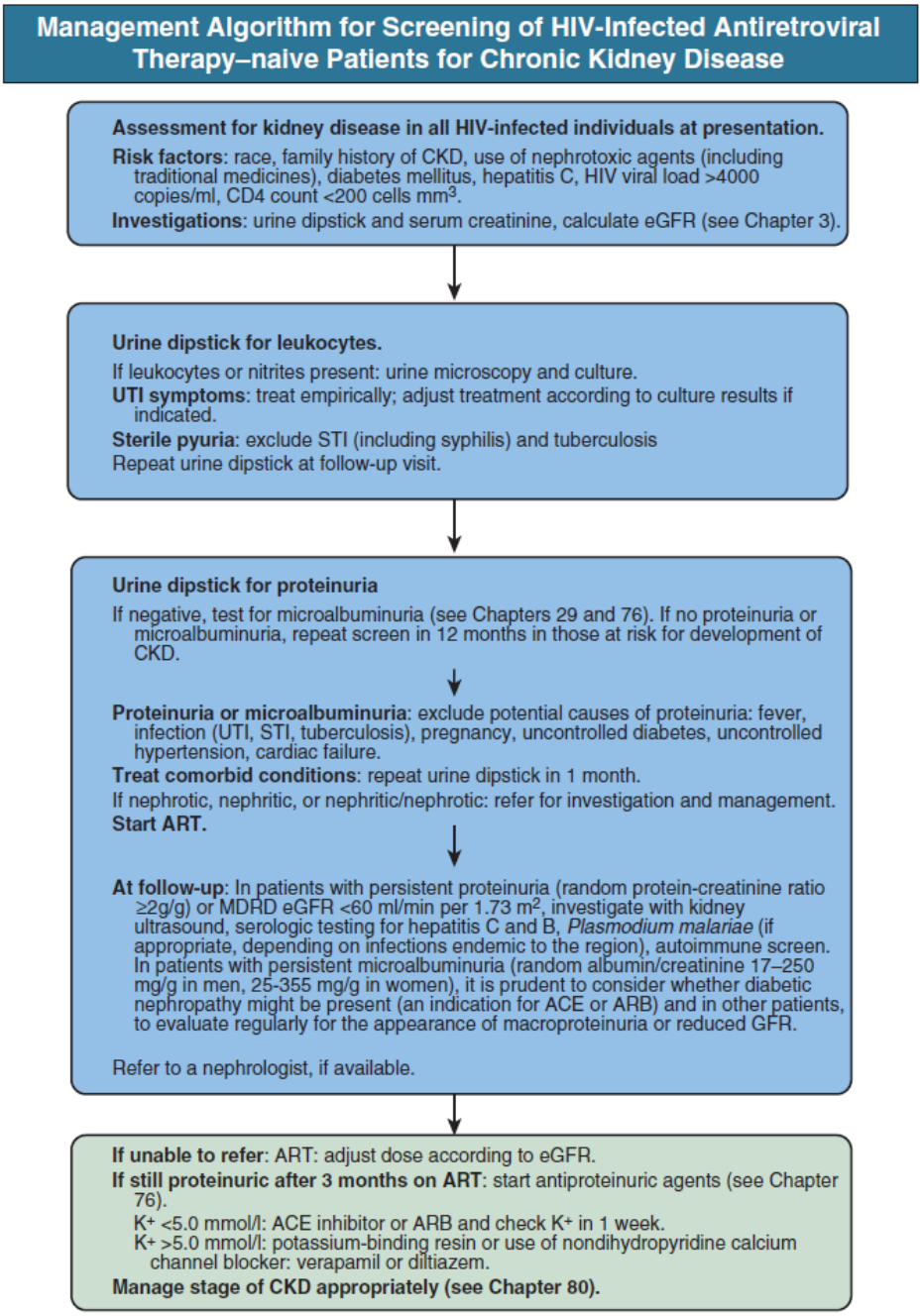
Risk factors for CKD can be classified as modifiable and non-modifiable. The non-modifiable risk factors include race, genetic predisposition and age. The main modifiable risk factors are[2]

- *Body weight*,
- *Concomitant illnesses* (hypertension, diabetes mellitus, chronic HBV or HCV),
- *Use of potentially toxic drugs* (ART: tenofovir, indinavir; Other: NSAIDs, aminoglycosides, amphotericin B, cidofovir, co-trimoxazole sulfadiazine, acyclovir, foscarnet),
- *HIV associated factors* (viral replication, CD4+ lymphocyte nadir <200 cells/µl, previous diagnosed AIDS).

By keeping the kidney function under control, one can detect renal disease early and adjust the therapy as needed. A basic renal study should include measuring of serum creatinine concentration and eGFR, protein/creatinine ratio (PCR) and albumin/creatinine ratio (ACR) in

the case of hypertension or diabetes, in the first morning urine. Urinary sediment and evaluation of tubular function should also be investigated.[2]

Table 3. Management algorithm for screening of human immunodeficiency virus (HIV)-infected antiretrociral therapy-naive patients for chronic kidney disease. Tuberculosis may be pulmonary or extrapulmonary. Antiproteinuric agents may be used in normotensive individuals with gradual uptitration of dose, depending on tolerance and severity of proteinuria. eGFR calculated by CG or MDRD. According to Johnson RJ, Feehally J, Floege J (2015), p. 685



Creatinine Clearance and eGFR

Mocroft et al. compared the estimation of GFR using Cockroft-Gault (CG) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations in HIV infection to see if anyone correlated better with kidney function, end-stage renal disease or deaths from kidney disease and all-cause mortality.[55] The two most used formulae today are the Modification of Diet in Renal Disease (MDRD) and the CKD-EPI, which estimate the glomerular filtration rate[56], whereas the Cockroft-Gault formula estimates creatinine clearance. The authors measured eGFR in 133 873 patients with CK standardized for body surface area (BSA) and CKD-EPI and out of them 85.7% were the same with both formulae. The agreement was considerably lower when CK was not standardized for BSA. The cases with discordant measures were more common in those co-infected with HCV, the non-white and those with unknown HIV exposure. In conclusion, they found that CG and CKD-EPI performed equally well in predicting ESRD and all-cause mortality.[55] Levey et al. found that CKD-EPI was better at estimating GFR than MDRD, especially at higher levels and thus allowing earlier detection and intervention.[57] The CG have traditionally been used to calculate drug dosages, using serum creatinine concentrations[58]. Although with limited studies performed on eGFR as measurement, some suggest that MDRD gives a good estimation for drug adjustments and can be used instead of CG.[59, 60]

Protein/creatinine (PCR) or albumin/creatinine ratio (ACR)

Small increases in proteinuria usually precede an increase in serum creatinine and decrease in GFR. Gupta et al. found a correlation with proteinuria in first urine and development of ESRD.[61] Szczech et al. noticed that up to 30 % of their subjects had proteinuria and found risk factors to be elevated HIV RNA level, low CD4+ cell count (<200cells/mm^3), black race, and the presence of HCV antibodies.[62] Hypoalbuminemia was identified as an independent risk factor for the development of ESRD, just as the previously mentioned HIV-associated factors, hypertension, diabetes and cardiovascular disease.[63] This shows the clinical significance of following the PCR or ACR. There are different types of proteinuria and it is important to differentiate them.

- *Glomerular proteinuria*: Proteins found in urine are mostly albumin, commonly caused by hypertension and diabetes.
- *Tubular proteinuria*: This type of proteinuria is secondary to tubular toxicity and more often associated with antiretroviral therapy. Proteins found in the urine are usually of

low molecular weight such as α_1-microglobulin, β_2-microgloblin, retinol-binding protein, n-acetyl β-glucosamidase or neutrophil gelatinase-associated lipocalin.

- *Mixed proteinuria*: This occurs when there is co-existence of both pathogenic processes.

The procedures for measuring protein in urine are more sensitive for albumin than low molecular weight proteins, which must be present in fairly high concentrations to be detected.[64, 65] In a study carried out in HIV positive patients, 21% of patients with proteinuria >300mg/g did not test positive with the test strip, but with but were detected when using PCR.[66] Many laboratories do not have the technology to detect low molecular weight proteins and the use of ACR can distinguish protein of glomerular origin from that of tubular. By expressing protein content in urine in ratios, estimation errors from using dilute samples can be avoided.[2, 67]

Renal replacement therapy (RRT)

Until 2001, chronic dialysis was the only available treatment for HIV-positive patients with ESRD in the United States. In Kumar et al. they found that the patient survival at one and two year post transplant was 85 % and 82 % respectively[68], whereas studies of survival of HIV-positive patients on dialysis have been found to be much lower, 58% and 41% at one and three years respectively.[69] Between 1990 and 1999, the 1 year survival of HIV-infected patients on dialysis improved from 56% to 74%. Ahuja et al. investigated the survival of HIV positive patients on dialysis to see if the improved survival in the whole population after introduction of HAART applied to those on RRT as well. Until this time RRT did not seem to provide any survival benefit in patients with AIDS, but only in those with still asymptomatic HIV. The poor survival rate made it questionable whether to put HIV infected patients on RRT at all.[70] The study showed that survival improved from 1997 (two years after HAART was introduced and the same year as it became treatment standard) and onward, but not to the same proportion as in the HIV-negative dialysis patients. One possible mechanism could have been the unknown pharmacokinetic effects of the ART in dialysis.[69] Trullás et al. made a nationwide multicenter retrospective cohort study of HIV-infected patients on dialysis between 1999 and 2006 in Spain. The subjects were matched with a control group for age, year of starting dialysis, sex, race and dialysis center. The HIV-positive patients five year survival was lower than their HIV-negative counterpart 62.7% and 94.4 %, respectively. The

HIV-positive group was also less likely to be put on the waiting list for transplantation, 17% versus 64 % and less likely to be transplanted.[71]

Antiretroviral dosing in patients with renal dysfunction/on dialysis

Today there are guidelines on how to adjust dosing of ART in patients with decreased kidney function; both for those with primary ESRD and those who already received a kidney transplant but later again experienced deteriorating function. The majority of proton pump inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized by the liver and does not require any adjustment in kidney disease.[72] The NRTIs on the other hand are mainly eliminated by the kidneys, both by glomerular filtration and tubular secretion. Dose adjustment in patients with impaired kidney function is important because some of them have nephrotoxic effects, e.g. Tenofovir. NNRTIs do not bind to proteins to a large extent and thus are easily removed by dialysis. PIs on the other hand are extensively bound to plasma proteins and cannot be cleared by dialysis. In Spain HIV-positive patients represent about 0.5% of all patients on dialysis.[2] The majority are on hemodialysis, but no survival benefit has in general been reported in either hemodialysis or peritoneal type.[73]

Renal transplantation

The history of organ transplantation started in 1906 when kidneys from different animals were used. Thirty years later human cadaveric kidney transplantation was tried, but it failed due to the fact that the donor and recipient had different blood type. In 1944, the British scientist, Sir Peter Medawar, discovered that rejection was due to immunologic factors and paved the way for the first successful kidney transplantation in 1954[74]. It was performed on identical twins at the Peter Bent Brigham Hospital, in the United States. After this, other organ transplantations followed with improvements in technique and immunosuppressive therapy. In 1983, cyclosporine was approved by FDA and, when administered with corticosteroids, it revolutionized the transplantation medicine. In 1994, tacrolimus was approved further improving outcome and decreasing side effects. In the mid 1990's the question about living donor transplantations was raised due to the organ scarcity. Mycophenolate mofetil was added to the market of immunosuppressives in 1995 and in 1999 sirolimus also. In 2001, the number of living donor organ donations surpassed cadaveric transplantation for the first time in the U.S.[75]

Eligibility for the waiting list

Spital et al. sent out a questionnaire in 1998 to 248 transplantation centers in the U.S. regarding their willingness to put an HIV positive person on the waiting list. All centers answered that they required an HIV test prior to considering transplantation. The result from the questionnaire showed that an HIV-positive patient, who would otherwise be considered good candidates, would be denied a cadaveric transplant in 88 % of the centers and a living transplant in 91 %.[76] The poor outcomes reported before the HAART-era made their impression on the transplant community and for a long time it was questionable as to whether or not it was morally acceptable to perform such invasive procedure with low chance of success implied that it would be a waste of organs. [41, 68, 77] The later trials showed good outcomes and similar results to the general population was slowly changed the attitude towards transplantation in the HIV-infected. Now, many guidelines recommend transplantation in the carefully selected patient.[2 72]

Sawinski et al.reported that HIV-positive patients are less likely to be put on the waiting list for a transplant. Only 20% of theoretical HIV-positive patients were included on the list compared to 70% in the HIV-negative group over the same period of time. They examined the barriers and found several possible factors for this, including lack of documentation of HIV control, CD4+ <200cells/ml^3, history of drug use, and African American race[78]. According to the Scientific Registry of Transplant Recipients (SRTR) among the HIV-positive recipients only 33 % of the recipients of living donor organs and 42 % of cadaveric donor organs were of African American descent[79] although they tend to represent over 80 % of the persons with ESRD within the HIV-positive population.[80]

Specific clinical criteria in the HIV-positive patient considered to be important for a successful transplantation are[79]

- Be free of opportunistic infections
- Compliant with therapy
- Controlled with cART
- Control of CD4+ count > 200 cells/mm^3 for at least six months prior to transplantation
- Patients with HBV or HCV co-infection need an additional evaluation by a hepatologist to ensure good liver synthetic function prior to kidney transplantation

- Absence of opportunistic infections or malignancy including a history of progressive multifocal leukoencephalopathy, lymphoma, pulmonary aspergillosis, significant Kaposi sarcoma, or coccidiomycosis, but every case should be evaluated individually

A history of opportunistic infections is not necessarily a contraindication, but those mentioned in the paragraph are since these cannot be treated in an immunocompromised patient.[41] The CD4+ cell count is an important marker of success, with the limit generally set on 200 cells/mm^3 for four to six months prior to the transplant and the HIV-RNA should be undetectable, at least <50 cells/ml.[77] Ideally the patient should not have had an AIDS-defining event and had a psychiatric evaluation. Inclusion criteria for the waiting list are an HIV-infected individual with CKD on RRT or in pre-dialysis phase who meet the general criteria after renal transplantation evaluation and HIV-specific criteria are passed.[2]

Rodrigue et al. examined the willingness of HIV-positive patients to pursue living donor kidney transplantation (LDKT) in comparison to non-infected.[81] Standardized questionnaires were given to HIV-infected and one non-infected control, matched by year of evaluation, age, sex, race and waiting time was included in the study. They found that the non-infected patients were mostly concerned if they would die if a living donor could not be found. The HIV-positive patients were concerned that no one would volunteer to be a living donor and they would feel guilty if a possible donor was found. They were afraid that the donor of the transplant would be pressured to donating or that the transplant center would be angry with family members if they would not agree to donate. In addition, the HIV-positive group had less knowledge about transplantation and donors than their non-infected counterpart. This included information about donor status, how quickly a donor can return to work, and that kidney donation typically does not increase the risk of future kidney failure. In the non-infected group, 42% considered LDKT, compared to 21 % in the HIV-positive group.[81] Some transplant programs require disclosure of HIV status to potential donors, whereas others do not. The social stigma of having HIV is still very much present today and the study found that most of the patients saw their HIV-status as a barrier to LDKT and felt uncomfortable sharing this information with a potential donor.[82, 83] The lack of knowledge regarding living donor kidney transplant surprised the authors since the same information was offered to everyone regardless of HIV-status and they speculated that it might reflect their reluctance to pursue this option due to the perceived barrier of their infection. Another fact that stood out was that most HIV-positive patients did not know the current outcomes after kidney transplantation and might therefore be less likely to consider it. The fear of having to disclose their HIV

status, limited knowledge about the possibilities and outcomes of transplantation, and social stigma seem to explain why HIV infected patients are less likely to consider LDKT.[81]

The impact of immunosuppression on HIV replication

A reason many did not consider renal transplantation in the HIV-positive patient is the notion that the post-transplant immunosuppressive therapy would lead to progression of the HIV disease.[84] Further studies on the action of immunosuppressive therapy (IS) in HIV-infected patients provided a reason to believe otherwise. IS could, by disrupting infection of cells by HIV virions or by suppressing T-cell activation, even be beneficial in this patient group.[79]
The human immunodeficiency virus infects a memory CD4+ T-cell with a concomitant CCR5 expressed on the cell surface. The central pool of CD4+ cells does not express CCR5 and are relatively protected from infection until they become activated. As the cells are infected pro-inflammatory cytokines are released and during chronic HIV-infection there is continuous immune hyperactivation of T-cells.[85] The persistent viremia together with the consequent depletion of CD4+/CCR5 cells seems to be especially prominent in the gut mucosa (GALT) leading to translocation of bacteria through the intestinal epithelium. This exposes the patient to inflammatory mediators such as bacterial lipopolysaccharides further stimulating the ongoing immune reaction.[86] An antibody response can further worsen the situation by binding to the infected cells causing complement activation and immune complex deposition.[87] Even those effectively treated with ART have a continuous chronic inflammatory response which may be a cause of tissue damage.[79]

Studies have shown that the cellular protein cyclophilin A is required for maturation of the HIV-1 and subsequently for its ability to infect other cells.[88, 89] Both cyclosporin A (CsA) and tacrolimus (Tac) have been demonstrated to impact HIV replication. In vitro studies showed how CsA binds to cyclophilin A and suppresses IL-2 mediated lymphocyte activation, decreases infectivity of naive cells and inhibits viral production in chronically infected cells.[90] Tac interfere only with growth of chronically infected cells, but do not decrease infectivity as seen with CsA.[91] Sirolimus reduces CCR5 expression and causes suppression of the HIV-1 replication in vitro at concentrations far lower than the therapeutic dose for immunosuppression in kidney transplantat recipients.[92]
One study compared the treatment of patients newly diagnosed HIV treated with only HAART and a group treated with HAART and concomitant cyclosporin A. At the end of the study viral replication was equally suppressed, but the CD4+ cell count was significantly

higher in the group treated with both HAART and cyclosporine. This finding suggests that immunosuppression prevent the inflammatory trigger to cause activation of central CD4+ cells and thus also prevent them from being infected, could have a beneficial effect.[84]

Outcome after transplantation

In the pre-HAART era, the outcome after solid organ transplantation in the HIV-infected patient was poor, leading to shorter AIDS-free interval and frequently death due to AIDS or AIDS-related complications.[93-95] The pilot study performed by Stock et al. in 2007 challenged the odds of the previous reports. This was done in the setting of better control of HIV, since the introduction of HAART in 1996, and more effective prophylaxis and management of opportunistic infections.[96]

Kumar et al. performed one of the earlier studies on the outcome of renal transplantation in the HIV-positive group. Clinical acute rejection occurred more frequently than in the non-HIV group and they speculated that the reason might be that they used lower level of immunosuppression to avoid opportunistic infections. Ultimately the graft survival was comparable to other high risk groups, and the patients had better survival than those who were maintained on dialysis. They noted that the majority of their subjects were African-American (97%) and that half of the kidneys came from marginal donors[68], factors that on their own are associated with a lower rate of graft survival.[97]

Qiu et al. used information from the UNOS Renal transplant registry to study the outcome after renal transplantation when one of the donor kidneys went to a HIV-positive recipient and the other to a HIV-negative recipient. Although they admitted low power, the study showed a statistically significant survival rate that was similar in both patient groups. The survival was even slightly better in the HIV-positive group, possibly due to stricter selection criteria, the fact that they in general were younger or that they had lower levels of PRA. The HIV-positive cohort had higher creatinine values which could be due to the nephrotoxic effect of ART that can occur with the intricate interactions with the immunosuppressive therapy.[98]

Roland et al. conducted a prospective study of liver and kidney transplantation in the HIV-infected patients and recorded the patient, graft and HIV related outcomes. With a median follow up of three years, patient survival was approximately 94 % and graft survival was 83 % after one and 3 years, respectively. The reasons for rejection were severe acute rejection, chronic rejection and vascular thrombosis. Both patient and graft survival were similar to the general population transplanted at the age of 65 or older, as reported from the Organ

Procurement and Transplantation Network (OTPN)[99]. Candida esophagitis was reported in one patient with diabetes, previously treated with thymoglobulin for an event of acute rejection, but who recovered with antifungal treatment. The cumulative incidence of allograft rejection at 1, 2 and 3 year reached 52 % in the kidney transplant recipients. Hazard ratios were increased and found statistically significant only for age and panel reactive antibodies (PRA) levels at transplant. Other factors, such as most recent CD4+ cell count, antigen mismatch, use of ART and delayed initiation of cyclosporine were speculated to have influence, but could not be proven due to the low power of the study. They made the observation that the patients with episodes of rejection had a higher median creatinine value.[100]

The Croatian case report shows similar results with an HIV-infected patient under good control prior to transplantation, standard induction therapy (prednisolone, tacrolimus, mycophenolate mofetil and basiliximab). The patient experienced coagulation abnormalities with bleeding despite normal coagulogram, Non ST-elevation myocardial infarction (NSTEMI), psuedomonas pneumonia and borderline acute rejection requiring a period of dialysis. The patient improved with three boluses of methylprednisolone and was ready for discharge two months after transplantation. The patient was under the care of a multidisciplinary team with nephrologists, urologists and infectologists.[101]
An evidence-based analysis on the outcome of solid organ transplantation in the HIV-positive patient concluded that the risk of death after kidney transplantation did not differ between HIV-positive and -negative patients although they found the level of evidence to be very low. The same low evidence made the result of insignificant difference in risk of acute rejection between HIV-positive and HIV-negative uncertain.[102]

Infection

The majority of infections reported after kidney transplantation have typically not been opportunistic in nature,[68, 96] but the use of thymoglobulin has been associated with opportunistic infections in several studies.[96, 100]
Proper prophylaxis against opportunistic infections is essential. Today these include cytomegalovirus, toxoplasmosis, pneumocystis carinii pneumoniae, mycobacterium avium complex, cryptococcosis and histoplasmosis.[41] Additionally recommended prophylaxis include tuberculosis, hepatitis A and B, *Streptococcus pneumoniae,* chicken pox and *Hemophilus influenzae B.*[77]

Table 4. Opportunistic infections and their treatment. **Reproduced with the permission from Wolters Kluwer Health.**[41]

Condition	Primary prophylaxis[a]	Secondary prophylaxis[b]
Pneumocystis carinii pneumonia	Indicated for life; Initiate immediately posttransplant Preferred: TMP-SMX Alternative: dapsone, if not G6PD deficient, atovaquone	Indicated for life; Initiate immediately posttransplant Preferred: TMP-SMX Alternative: Dapsone if not G6PD deficient, atovaquone
Toxoplasmosis	Toxoplasmosis IgG-positive patients with CD4+ T cell count ≤ 200 Preferred: TMP-SMX Alternative: atovaquone, sulfadiazine + pyrimethamine + leucovorin	CD4+ T cell count <200 cells/mL. Discontinue when CD4+ cell count is >200 cells/mL for 3-6 months Alternative: atovaquone, sulfadiazine + pyrimethamine + leucovorin
Mycobacterium avium complex	Indicated when CD4+ T cell count is ≤ 50 cells/mL. Discontinue when CD4 count is above 100 cells/mL for 3-6 months. Preferred: azithromycin 1200mg weekly Alternative: clarithromycin	Cell count 50 cells/mL Discontinue when CD4 count is above 100 cells/mL for 3-6 months. Alternative: clarithromycin ' ethambutol
Cytomegalovirus	No HIV-specific indication	Cell count 75-100 cells/mL Discontinue when CD4+ T cell count is above 100-200 cells/mL for 3-6 months. Preferred: valganciclovir Alternative: foscarnet, cidofovir
Cryptococcosis, extrapulmonary	No HIV-specific indication	CD4+ cell count below 200 cells/mL. Discontinue when CD4+ cell count is above 200 cells/mL for 3-6 months[c] Fluconazole
Histoplasmosis	No HIV-specific indication	Continue regardless of CD4+ cell count Itroconazole

- *a* No history of the infection
- *b* Prior history of the infection
- *c* Secondary prophylaxis should also be reinstitued immediately posttransplant for 1 month and during the treatment of acute rejection for 1 month following completion of acute rejection therapy. If the CD4+ T cell count is suppressed, continuation should be guided by the CD4+ T cell count.

Rejection

The rate of rejection is much higher than in that of the general population, sometimes as high as two or three times. Despite this number, the overall graft survival is not different from the non-HIV transplanted.[77] It is believed that the immune system of an HIV positive patient is dysregulated rather than just suppressed. This is supposed to be the cause at least in the cases of very early rejection.[96] Another theory is that the complex drug interactions cause fluctuations in the blood concentrations of the immunosuppressive therapy opening up to

rejection.[96, 100] Today, most of the episodes of rejections are susceptible to therapy with either corticosteroids or, in more severe cases, thymoglobulin.[79]

Drug interactions

Drug interactions between IS and ART are a big concern in the transplanted HIV patients. The interactions are unpredictable and are not the same even within groups of ARTs. The impact of these uncertain drug levels can lead to either toxicity or suboptimal immunosuppression. The main interactions seem to be between calcineurin inhibitors (CNI) and protease inhibitors (PI). Many of the PIs inhibit CYP-450 3A, which are responsible for metabolizing both immunosuppressants and other ARTs.[103] The efflux transporter P-glycoprotein (P-gp) is predominantly found on the apical side of intestinal and hepatic epithelial cells and act to decrease absorption and increase excretion of its substrates. Normally in intestinal cells, P-gp and CYP3A4 act to decrease absorption and increase drug metabolism. Concomitant administration of immunosuppressant and ART acting on these processes is expected to decrease their metabolism while increasing their uptake, leading to higher systemic blood levels.[104] P-glycoproteinis is another substrate for the PIs[105]. Frassetto et al. 2013 described the pharmacokinetics of concomitant administration of ART and IS in a longitudinal study. In the first three months after transplant when CsA was given together with a PI only 1/10 of the dose necessary for the non-HIV patients was enough to reach therapeutic blood levels. The dose of CsA had to be higher when given with Efivirenz (EFV) than when given together with Nevirapine (NVP), and both were significantly higher than if it was administered with PIs in week 2-12. Bioavailability of CsA, when given concomitantly with EFV increased over time, whereas there was no time dependent change when co-administered with PIs or NVP. In a combination dose of PI+NVP the CsA dose increased by about 30 % with almost unchanged AUC. With tacrolimus the dose had to be lowered significantly when given together with PIs with exposure increasing 10-fold, but was not affected significantly by NVP or EFV. The increased bioavailability of TAC with PI was significantly higher than for CsA.[104]

A higher level of IS is associated with a lower risk of rejection. Frasetto et a. found that giving a PI (CYP450 inhibitor) and a non nucleoside reverse transcriptase inhibitor (NNRTI) (CYP450 inducer) together, did not produce the estimated intermediate effect on the IS metabolism. Due to different potencies, the additional effect on the P-gp and probably several unknown transporters, the resulting trough levels are unpredictable. The conclusion was that

EFV and NVP affected CsA differently over time, making predictions according to group inaccurate.[104]

When using PIs and CNIs, the dosages of CNIs must be significantly reduced or the dosing free intervals extended. Tacrolimus is a substrate for both CYP 450 3A and P-glycoprotein. The latter is responsible for the drug's entry into lymphocytes, through the blood brain barrier and into tissues. There seems to be almost identical features with cyclosporine, but it has been less extensively tested in vitro. There are also studies showing different tacrolimus drug interactions between gender and ethnicities.[106] Sirolimus and Everolimus are also substrates for P-450 and P-glycoprotein and have been reported to react similarly, but only limited data exist.[107]

The non-nucleoside reverse transcriptase inhibitors NNRTs are p-450 substrate inducers and can lead to increased metabolism of CNIs or sirolimus with consequent sub-optimal levels in the blood.[107] The NRTs are not substrates for the p-450 system, but may contribute to both anemia and neutropenia. This together with the effect of some immunosuppressive drugs, may cause severe leukopenia and CD4+ cell depletion.[79]

The active metabolite of MMF, mycophenolic acid, interferes with the conversion of inosine monophosphate (IMP) to guanosine monophosphate (GMP). Some in vitro studies showed several interactions between MMF and ART, including abacavir, didanosine and tenofovir.[79] Apart from its interactions it seems as though the depletion of GMP, the substrate for reverse transcriptase in the virus infected cells, might prevent replication of the virus and even induce apoptosis of activated CD4+ cells in vitro with the result of hampering the infection.[109] Glucocorticoids are, like the NNRTs, inducers of the p-450 system. The tapering of the steroid dose that typically starts after transplantation may be accompanied by changes with increased blood concentrations of CNIs and decreased CD4+ cell counts. This consequently puts the patient at a higher risk of nephrotoxicity and infection.[109]

Drug selection in the transplant recipient

Different immunosuppressive regimens have been tried and so far there is no convincing evidence that one is superior to the other.[77] In addition to the usual challenge of balancing the risk of rejection and opportunistic infections this patient group have the drug interactions between the immunosuppressants and the ART.[79] For the induction therapy, many are trying

to avoid lymphocyte-depleting drugs, e.g. thymoglobulin, because it can cause a very low CD4+ T cell count for an unpredictable duration of time[77]. Several authors have noticed an increased frequency of infections with this drug.[96] High immunologic risk patients usually receive a more aggressive induction therapy pre-transplantation; typically they receive antithymocyte globulin or an IL-1 receptor antibody.[110] The use of glucocorticoids and IL-2-inhibitors made lymphocyte-depleting drug-sparing regimens possible.[77]

The maintenance therapy today typically consists of three components: a CNI (e.g. cyclosporine or tacrolimus), an anti-metabolite (e.g. mycophenolate mofetil) and corticosteroids.[77,79] CsA is commonly favored because of its positive effect on both antiretroviral and immunosuppressive effects.[79, 90, 91] It has been preferred over TAC in part due to the latter having an increased risk of inducing glucose intolerance, [77, 96, 101] but recent evidence suggests that CsA is associated with rejection episodes, although without loss of graft.[98] MMF deplete intracellular nucleotides and thus have antriretroviral properties and synergistic effects with certain NRTs, such as didanosine and abacavir.[30, 77]

Sirolimus is, in addition to downregulating the CCR5 expression, an anti-proliferative agent that is useful in the treatment of Kaposi sarcoma and it has been suggested that it could be used beneficially in cancer occurring post-transplant. It can be a good alternative in those experiencing cyclosporine toxicity or decreased renal function of other etiology.[77]

There are five groups of antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTIS), protease inhibitors (PI), entrance inhibitors and integrase inhibitors. Usually a combination of three is used and the goal is to set a regimen that can be continued post-transplantation. Tenofovir is associated with both acute and chronic declines in renal function and should be used with caution in transplant recipients.[79] Combination pills usually have to be avoided in patients with impaired kidney function due to the need to individualize dosing regimens of the different drugs and requirement to adjust them over time.[104]

CCR5 is a co-receptor needed for HIV to infect CD4+ T cells and those who are homozygous for CCR5Δ32 mutation causing a non-functioning receptor are resistant to HIV infection. This receptor was found to be upregulated in cases of acute rejection and drugs deactivating this receptor has become of interest in transplantation medicine.[113] Fischereder et al. studied the outcomes after renal transplantation in patients homozygous for CCR5Δ32 mutation, heterozygous and homozygous wild-type. The results were statistically significant with improved graft survival in the CCR5Δ32 homozygous group compared to the heterozygous and those with wild-type mutation.[112] Heidelhain et al. got similar results.[113] The CCR5-

antagonist maraviroc, (ART), was tested in patients receiving hematopoietic stem cell transplantation (HSCT) and proved to have lower incidence of visceral GVHD. Maraviroc hampers chemotaxis without interfering with the function of the T cells.[114]

Corticosteroid-sparing regimen

Corticosteroids are a part of the maintenance therapy after transplantation in many regimens, but have an increased risk of cardiovascular events.[115] Early withdrawal regimens have been tried in HIV-negative kidney transplantation. Knight et al. performed a meta-analysis of kidney transplantation where steroid avoidance or withdrawal (SAW) protocol had been followed. They found an increased risk of acute rejection episodes, although with only a marginal effect on graft survival and that cardiovascular risk factors, measured by HTN, DM and hypercholesterolemia, were greatly decreased.[116] Very early steroid withdrawal (VESW), when corticosteroids is removed before day three post-transplantation, was studied. In a meta-analysis of RCTs of renal transplantations and VESW protocol, an increased rate of acute rejection was found, although they were mild episodes that were mostly amenable to therapy. They found that this difference lost significance for the patients receiving TAC, but maintained for those on CsA. VESW was associated with delayed graft function (DGF). Cardiovascular risk factors were significantly reduced with this protocol. In conclusion it was safe to withdraw corticosteroids early, but longer than three days would decrease the risk of DGF.[117] Muthukumar et al. tried SAW in the kidney transplantations of 11 consecutive HIV-infected patients. The authors used an anti-thymocyte globulin agent as the primary induction agent, intravenous methylprednisolone day 0-4 and maintenance therapy with tacrolimus and mycophenolate mofetil without any corticosteroids. All patients were low-risk and maintained on HAART both before and after transplantation. One year patient survival was 100% and allograft was 91%; at three years it was 90% and 81 % respectively. One patient died of uncertain causes; it was believed to be of cardiovascular reason, but the subject had a stable graft function on the last check up. The causes of rejection were primary non-function and acute rejection. Two episodes of acute rejection were treated with pulse methylprednisolone, immunoglobulins and plasmapheresis, but both grafts failed despite this. No progression of HIV-disease was reported, measured by increased number of viral copies. Complications included infections and cancer, all successfully treated. Overall the graft and patient survival were comparable to larger studies done in the HIV-positive population with non-steroid sparing treatment and with seemingly reduced cardiovascular risk. No patient had any change in weight, blood pressure or lipid lowering drugs and no new onset of diabetes mellitus after

transplant (NODAT). The results were promising, but should be interpreted with caution due to its low power and lack of control group.[118]

Combined liver and kidney transplantation in the HBV/HCV-HIV infected patient

Many patients with HIV are co-infected with HBV or HCV, in some studies as high as 50 %, due to a common route of transmission.[102] The infections affect each other; the HCV infection can promote an antibody-antigen complex glomerulonephritis and cause ESRD and the treatment of HIV with ART can hasten the progression to end-stage liver disease in the person with HCV-infection. The HCV/HIV co-infected patient has a poorer response to anti-hepatitis medication, mostly pegylated interferon (IFN) and ribavirin, and they have many interactions with ART. Post-renal transplantation immunosuppression is believed to activate HCV replication and accelerate the development of end-stage liver disease. Furthermore IFN therapy is contraindicated in the renal transplant patient.[119] End stage liver disease, many times due to HCV-infection and its sequelae (cirrhosis, liver failure and hepatocellular carcinoma) is now a leading non-AIDS cause of death in the HIV-positive patient in the developed world.[77,120] Patients with HIV-infection and concomitant liver failure have a poorer pre-transplant survival rate than the HIV-negative corresponding group.[121] HBV infection has no negative effect on graft- or patient survival after kidney transplantation. Patients with a co-infection of HCV have shown variable results after transplantation. The Ontario Health Technology Assessment Series evidence based analysis, made in 2010, found that the risk of death after transplantation was 2.8 times higher in the co-infected (HIV+/HCV+) than the mono-infected (HIV-/HCV+).[102] One study attributed the lower graft and patient survival to older age, combined liver-kidney transplantation, an anti-HCV-positive donor and a BMI <21kg/m^2. Without these factors the survival rates were the same as after transplantation in a HCV mono-infected patient. Many patients experience HCV recurrence following transplantation contributing to the lower survival.[77] The new anti-viral drugs for HCV, called direct-acting antivirals have so far limited experience, but show promising results. Concerns regarding drug-drug interactions with the HIV ART still exist.[122]

Eligibility criteria are somewhat different in this group than the monotransplant kidney patients; In some combined liver-kidney transplantations the viral load can be accepted to be higher if the patient cannot tolerate HAART due to poor liver function and drug associated hepatotoxicity. BMI should be > 21kg/m^2.[73]

Discussion

The history of HIV/AIDS is a relatively short one. It appeared in the 1980's and a diagnosis meant a certain and imminent death and today it can be considered to be a chronic disease. Many times the disease was associated with homosexuals, intravenous drug abusers and black people, but later spread to transplant recipients and other groups of society. Since the introduction of the first anti-HIV drug in 1987, and later HAART in 1995, the future of HIV/AIDS patients changed quickly. In the developed world the morbidity in this population has become more similar to the general population with hypertension, diabetes and end-organ failure. This group is even more susceptible to these conditions due to side effects of the cART. Transplantation as treatment of end-organ failure in the HIV-positive patient has long been considered futile. There have been many and major obstacles to successful transplantation, but they are being overcome one at the time. In the beginning the short life span of the infected person made transplantation a dangerous procedure that did not improve neither the quality of life nor the possibility of survival of the patient and was thus considered a waste of scarce organs. Many feared that the immunosuppression from the transplantation therapy would cause unlimited viral replication and hasten the progression to AIDS and death. HAART allowed better controlled HIV and some started performing transplantation in well regulated patients. The results were significantly better than before, but still lower than the general population. It was speculated that this could be because they received suboptimal immunosuppression, organs from marginal donors and that they were mostly Black, all which historically were associated with a poorer outcome. The realization that immunosuppressive treatment might actually have a beneficial effect on HIV has increased the willingness to perform transplantation in this group. With time knowledge, novel drugs and treatment regimens, and experience of the treating physicians from all relevant fields in medicine led to better results. Still, acute rejection episodes are more common in this population, but are rarely leading to graft failure.

The HIV-positive patient population with ESRD, who require and is eligible for transplantation, is still relatively small and scattered over the world, making it difficult to attain large power studies to provide strong evidence. The research that are done using information from bigger data registries often encounter problems of missing data and inconsistent use of parameters, making comparisons difficult.

One of the issues today regarding transplantation is concerning optimal drug regimen. Complex drug interactions that are different between and within groups of drugs regarding

metabolism, excretion and bioavailability require regular and continuous checkups of drug concentrations in blood. A multidisciplinary team including infectious disease specialists and nephrologists is recommended for a better understanding and an optimal choice of drugs. The improved survival rates and graft function have allowed cardiovascular and other long term risk factors to be taken into account and different types of early corticosteroid withdrawal protocols are being tried.

An HIV-positive patient with end-organ failure is less likely to end up on the transplant list than his HIV-negative counterpart. The diagnosis of HIV is associated with a social stigma that can lead to less HIV positive patients to receive transplants. In countries like the United States, with a large Black population there is an underrepresentation of this subgroup even within the HIV-positive transplant recipients. Reluctance to revealing their HIV status to the donor and less awareness of the benefits of this treatment option were identified as possible causes. Specialized support groups and educational programs might be needed for these patients to learn about their options and be able to consider transplantation in light of the current research.

Conclusion

The studies performed with renal transplantation in the HIV-positive patients since the introduction of HAART has demonstrated continuously improving survival of both graft and patient, and today it is similar to those of the HIV-negative population. The question of whether it is beneficial to perform renal transplantation in the HIV-positive population were affirmative in the later studies, reviews and meta-analyses although they all admitted to low power due to small study sample sizes. In conclusion, more research has to be done to gain greater level of evidence, but regarding the disease and its management we have come to a point where the outcome of renal transplantation is similar to the general population and should be offered to anyone fulfilling the criteria.

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Biography

Emma Eliasson was born in Stockholm, Sweden in 1988. She lived there up until she was 21 years old and moved to Croatia to study medicine. After her first year she had a short internship in Addis Cardiac Hospital in Addis Abbeba, Ethiopia. During the summers she worked with people with psychiatric disabilities, children with neurological disabilities and as a personal aid. She worked as a student demonstrator in the course propadeutics on the nephrology department under the mentorship of prof. dr. sc. Bašić-Jukić and in 2014 they published an article on the outcome of renal transplantation in patients with HIV treated at KBC Zagreb together.