Renal Complications in HIV Disease: Between Present and Future

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Abstract

The recent introduction of new antiretroviral drugs, characterized by high efficiency and improved safety profiles, has not reduced the incidence of long-term adverse effects, in some cases manifested as selective organ damage. The presence of organ damage in patients receiving antiretroviral treatment is not only the expression of treatment toxicity, but also a complex interaction between individual risk factors, HIV-correlated effects, and antiretroviral drug toxicity. Kidney damage belongs to these adverse events. Renal function abnormalities are present in a large percentage of patients with HIV infection. Moreover, HIV-associated renal disease seems to be associated with progression to AIDS and death. In this review we address the various aspects of the epidemiology of renal damage, the interaction and the convergent effect of HIV and antiretroviral drugs in the onset of kidney injury, the interplay between kidney function and other organ systems, early clinical management, the monitoring of renal function, and a proposal of clinical approach to kidney disease in daily practice. Finally, we discuss future perspectives of renal damage in HIV patients and evaluate the patient’s perspective. (AIDS Rev. 2012;14:37-53)

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Key words


Introduction

The last decade has been witness to a radical change in the management of HIV disease. The first generation of antiretroviral drugs was burdened by a high degree of toxicity. The recent introduction of new molecules, characterized by high efficiency and improved safety profiles, has not reduced the incidence of long-term adverse effects, in some cases manifested as selective organ damage, but in most cases as a systemic premature aging that seems to characterize HIV-positive patients1-3. This phenomenon is also known to occur in other chronic inflammatory diseases4.

Therefore, the presence of organ damage in patients receiving antiretroviral treatment is not only the expression of treatment toxicity, but also a complex interaction between individual risk factors, HIV-correlated effects, and antiretroviral drug toxicity. These long-term adverse events are currently defined as “non-infectious HIV-related comorbidities”. 
Kidney damage belongs to these adverse events. Renal function abnormalities are present in a large percentage of patients with HIV infection. HIV-associated renal disease has become a relatively frequent cause of end-stage renal disease (ESRD) requiring dialysis and seems to be associated with progression to AIDS and death. In this review we address the multifaceted aspects of the epidemiology of renal damage, the complex interaction and the convergent effect of HIV and antiretroviral drugs in the onset of kidney injury, the interplay between kidney function and other organ systems, early clinical management, the possibility of a more thorough monitoring of renal function, and a proposed clinical approach to kidney disease in daily practice. Last but not least, we discuss future perspectives of the renal damage in HIV patients, and we evaluate an important but frequently unrecognized issue: the patient’s perspective.

**Epidemiology**

Renal complications of HIV infection are becoming a major cause of morbidity and mortality. A survey conducted during the period 1995 through 1999 evidenced a decreasing proportion of cytomegalovirus disease (from 6.8 to 2.8%), wasting/cachexia (9.8 to 6.8%), and dementia/encephalopathy (6.3 to 3.9%), while sepsis/septic shock (from 9.2 to 13.4%), and diseases of the liver (4.9 to 11.6%), kidney (6.3 to 9.1%), and heart (4.2 to 6.9%) showed an increasing prevalence. The observed trends in the pre-1995 era confirmed a decrease in the incidence of non-tuberculous mycobacteriosis (7.1 to 3.1%) and Kaposi’s sarcoma (5.3 to 2.6%).

In 2003, the HERS study showed that laboratory renal abnormalities, together with clinical AIDS, HIV RNA, and CD4 cell count, were the main specific determinants of hospitalization rates.

Data from the HOPS cohort showed that among 6,945 HIV-infected patients followed for a median of 39.2 months, death rates fell from 7.0 deaths/100 person-years in 1996 to 1.3 deaths/100 person-years in 2004 (p = 0.008 for trend). Deaths that included AIDS-related causes decreased from 3.79/100 person-years in 1996 to 1.32/100 person-years in 2004 (p = 0.008). Proportional increases in deaths involving liver diseases, bacteremia/sepsis, gastrointestinal diseases, non-AIDS malignancies, and renal diseases were also reported (p ≤ 0.001, 0.017, 0.006, < 0.001, and 0.037, respectively).

Recent data from the Aquitaine cohort showed that the incidence rate of chronic renal failure was 1.27 cases per 100 person-years. It increased slightly over time: 1.9% at one year, 3.3% at two years, 4% at three years, and 4.4% at four years. Factors associated with higher incidence were female gender, older age, diabetes, hyperlipidemia, low CD4 lymphocyte count, and exposure to tenofovir.

A study conducted on an urban U.S. HIV population found evidence of CKD in 24% of the patients. Forty patients (10%) had CKD stage 1, 19 patients (4%) stage 2, 29 patients (7%) stage 3, four patients (1%) stage 4, and eight patients (2%) stage 5. Patients with CKD were more likely to be African American, older, and have AIDS, lower CD4 counts, and higher HIV viral loads. Chronic kidney disease was also commonly associated to hypertension, diabetes mellitus, or both. Indinavir or tenofovir exposure was also associated with CKD. In multivariate analysis, hypertension, African American race, or hypertension and diabetes were the only significant predictors of CKD. Renal biopsies were done in 10 patients; five had HIV-associated nephropathy.

On the other hand, laboratory renal alterations are frequent among HIV-positive patients: in a study enrolling 2,057 HIV-positive women, 32% (n = 671) had proteinuria by dipstick on initial evaluation. Predictors of proteinuria included increasing (log) HIV RNA level (OR: 1.05), black race (OR: 2.0), absolute CD4 lymphocytes count ≤ 200 cells/mm³ (OR: 1.41), and the presence of hepatitis C antibody (OR: 1.27; all p < 0.0001). Absolute CD4 lymphocyte count ≤ 200 cells/mm³ (HR: 3.57; p = 0.001), detectable HIV RNA level (HR: 2.33; p = 0.02), increased systolic blood pressure (HR: 1.02; p = 0.002), decreased albumin (HR: 3.33; p = 0.0001), and increased serum creatinine (HR: 1.67; p = 0.0001) were all associated with the development of renal failure. Finally, higher HIV RNA level and lower CD4 lymphocyte count correlated with the presence of proteinuria and occurrence of renal failure.
In another study conducted on 845 HIV-infected persons, 30% of the patients had proteinuria and 43% had estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m². Persons on HAART (63%) had a lower mean eGFR compared with naive patients (92.0 vs. 101.6). In multivariate analyses, significant predictors of eGFR decline were diagnoses of hypertension, hyperlipidemia, proteinuria, use of tenofovir or stavudine, and lower viral load. The conclusions of the authors were that despite a low prevalence of chronic renal failure among HIV-infected outpatients, there was a high prevalence of asymptomatic renal dysfunction that was significantly greater than that of a well-matched control population.

The association between age and increasing prevalence of CKD has relevant implications for the HIV-infected population owing to the progressive ageing of this patient population. In fact, over a short period of three years between 2001 and 2004, the percentage of all HIV cases in patients aged ≥ 50 years increased from 17 to 23%[13]. This trend is expected to continue over the next decade. The increasing prevalence of HIV in older patients is a result of longevity in patients treated with HAART as well as new primary infections in more advanced age. The toxicities associated with HAART may be worse in older HIV patients, particularly those with underlying renal or hepatic insufficiency. Comorbidities are more common in older than in younger patients and can impact on the management of HIV in the former.

In a recent Italian study, the incidence and predictors of a > 20% reduction in eGFR levels, or a decrease from ≥ 90 to < 90 ml/min/1.73 m² from pre-combination antiretroviral therapy were evaluated in a total of 1,505 patients; 24% had eGFR < 90 ml/min/1.73 m² at baseline. Age, female gender, diabetes, hypertension, and higher baseline CD4 count were all associated with a greater risk of eGFR < 90 ml/min/1.73 m². Ninety-six patients experienced a decrease in eGFR of > 20% from pre-combination antiretroviral therapy levels (6.8/100 person-years). Besides the general factors, current exposure to didanosine, tenofovir, and protease inhibitors (PI) were the major determinants[14].

Acute renal failure occurs commonly among hospitalized patients with HIV and is associated with CKD, liver disease, and increased mortality: among 52,580 HIV-infected patients discharged from hospital in 1995 and 25,114 in 2003, compared with uninfected patients, HIV-infected patients had an increased incidence of acute renal failure in both the pre-HAART and post-HAART eras. In the post-HAART cohort, acute renal failure was associated with traditional predictors such as age, diabetes mellitus, and CKD, as well as acute or chronic liver failure or hepatitis coinfection. Acute renal failure was associated with mortality among HIV-infected patients in the post-HAART era[15].

HIV-associated nephropathy (HIVAN) has massively influenced the epidemiology in the USA and, until now, only marginally Europe, although migratory flows could determine in the future an increase in the number of cases. In fact, over 85% of cases of HIVAN occur in African American patients and it represents the third leading cause of ESRD in blacks aged 20-64[16].

African Americans seem to have a more aggressive natural disease history. In a cohort in Baltimore, Maryland, the authors measured CKD incidence, GFR slope, and progression to ESRD in 3,332 African American and 927 white HIV-infected subjects. A total of 284 subjects developed CKD, 35% of whom subsequently developed ESRD. African American subjects were at slightly increased risk for incident CKD compared with white subjects. However, once CKD has been established, the African American subjects developed ESRD markedly faster than white subjects and, correspondingly, their GFR decline after diagnosis of CKD was sixfold more rapid. In the subset of African American subjects for whom kidney biopsy data were available, progression to ESRD was significantly faster, irrespective of the presence of HIVAN[17].

**HIV infection and renal involvement**

HIV infection may promote renal diseases. However, in the last years, due to the widespread employment of HAART, there has been a decline in renal involvement as a consequence of viral infection.

As seen above, HIVAN, the typical expression of HIV-related renal disease, is still a major concern, but is practically confined to the black population. The potential evolution towards ESRD has been significantly hampered by HAART[18] and, differently from the pre-HAART era, survival of patients requiring renal replacement therapy, including renal transplantation, is similar to that of non-HIV subjects. Typically, HIVAN is characterized by massive proteinuria that, generally speaking, is a major diagnostic and prognostic factor of renal involvement. In fact, this is a marker of renal inflammation and, at the same time, a prognostic indicator of increased cardiovascular risk[19]. Besides this specific disease, HIV patients may experience an acute deterioration of renal function, or acute kidney injury (AKI), for which the RIFLE[20] or AKIN[21] criteria have catego-
ized different clinical situations with a variable outcome. Major contributors to AKI typically include sepsis, viral load, and concomitant HBV- or HCV-related diseases, but a growing role is played by nephrotoxins and HAART. Microangiopathic factors contribute to acute and chronic kidney damage. Immune complex glomerulonephritides, such as IgA nephropathy or other forms, are common, especially in Caucasian patients. Selective tubular damage with clinical pictures of Fanconi’s syndrome, nephrogenic diabetes insipidus, or renal tubular acidosis is also associated to toxicity of some antiretrovirals such as indinavir, cidofovir, and most recently tenofovir. A summary of the spectrum of renal involvement in HIV is reported in table 1.

HIVAN, defined by renal biopsy or clinical criteria, occurs in less than 1-12% of black patients. It is characterized by a clinical appearance of nephrotic proteinuria, increased echogenicity of kidneys, lack of hypertension or relevant edema, and progressive renal failure. Histological examination of the renal biopsy specimen shows focal and segmental glomerulosclerosis, often the collapsing variant. A direct pathogenetic role of HIV has been ascertained; however, given the almost exclusive involvement of descendants from African ancestors, a genetic predisposition has been advocated and specific gene loci invoked, like the MYH9 locus on chromosome 22. The more rapid evolution toward ESRD seems to be dependent on the extent of the renal damage as ascertained by histological examination of renal biopsy and not the time of initiation of HAART.

A spectrum of other glomerulonephritides and renal diseases has been reported in HIV patients. Some of them, like immune complex glomerulonephritis, IgA nephropathy, or thrombotic microangiopathy, are strictly linked to the viral infection. For some other forms, like post-infectious glomerulonephritis, lupus-like nephritis or immunotactoid glomerulopathy, the association is less direct and needs to be sought in each individual case. Finally, the occurrence of interstitial nephritis or membranous nephropathy is unlikely linked pathogenetically to the HIV infection and may be just a concomitant association.

Microalbuminuria has been advocated as a risk factor for cardiovascular diseases (CVD) in diabetics, but its role in hypertensive nondiabetic patients is less clear. Studies conducted in HIV-infected individuals have shown that 9-20% of subjects present microalbuminuria and this prevalence is 2-5 times higher than in the control population. In general, microalbuminuria correlated with HIV-dependent factors or HAART, such as the longevity of infection or lower CD4 count, may be more frequent in patients taking nonnucleoside reverse transcriptase inhibitors (NNRTI) and may be linked to an immune activation state induced by the viral load, as documented by increased mean levels of β2-microglobulin. The HIV patients that present microalbuminuria are at increased risk to develop overt proteinuria. However, as in the general population,
microalbuminuria is also significantly linked to cardiovascular risk factors such as hypertension, diabetes, or insulin resistance. In summary, an increased prevalence of microalbuminuria occurs in HIV patients, probably triggered by the infection itself, and its epidemiological meaning carries all the potential of a predictor of CVD.

Acute kidney injury is very frequent in hospitalized HIV patients and, as reported before, the increased risk compared to noninfected patients has not been changed by the introduction of HAART. Eighteen percent of hospitalized HIV patients experience AKI as a complication, which determines a significant morbidity and mortality. Common risk factors for developing AKI are ethnicity (blacks more susceptible), other general and specific comorbidities (low CD4 count, longer exposure to HAART, and HCV coinfection) and previous CKD. The most relevant aspect is that AKI is associated with an increased incidence of CVD, heart failure, ESRD, or death, especially in those patients which experience a severe renal complication requiring dialytic support. The initiation of HIV care in specialized clinics significantly reduces the incidence of AKI episodes in ambulatory patients.

Chronic kidney disease, defined as eGFR < 60 ml/min/1.73 m², occurs more commonly in patients with an HIV-induced immune activation, adverse metabolic consequences of HAART and/or renal toxicity of HAART and is much more common in advanced immunodeficiency. In large cohorts, 2.4-10% of patients developed CKD; predictive factors were older age, lower CD4 count at nadir, and an AIDS-associated condition. While most of the black patients experienced CKD as a progression of HIVAN, in white subjects relevant factors were exposure to nephrotoxic drugs such as indinavir or tenofovir, besides a range of common comorbidities. On the other hand, in African HIV patients with advanced diseases and mild renal dysfunction, the introduction of HAART produced a significant overall improvement of renal function by about 20% after two years of treatment. However, some drugs used in the HAART regimen (tenofovir associated with PI) may favor a more rapid decline of renal function compared to other therapeutic protocols (tenofovir and NNRTI).

End-stage renal disease occurs as a progression of CKD. The rate of progression is faster in African American than white patients. Mathematical models have estimated a reduction of 38% of the evolution from AIDS to ESRD after the introduction of HAART in the mid-1990s, however, the absolute number of HIV patients requiring dialysis should linearly increase up to 2020, due to an increase in HIV infection among black patients. Survival of HIV patients requiring hemodialysis seems to be worse than that of noninfected patients, although a French national survey at the beginning of the new century has reported an equal survival rate after a two-year follow-up.

Kidney and other organs

In this section we will analyze the implications of kidney function over other organ systems. These implications can be relevant in a context such as that of HIV infection because of the linkage between the role of the virus, the general health status of the patient, and the toxicity of drugs.

The kidney is involved in many processes related to the vitamin D cycle, bone metabolism, and CVD. Remarkably, the renal 1α-hydroxilation of 25-hydroxy-cholecalciferol (25(OH)D) leads to the final activation of vitamin D into calcitriol, the so-called hormone D. As known, vitamin D regulates phosphate metabolism both by favoring its gastrointestinal absorption and accumulation in bone, but it also decreases renal excretion. As a consequence, vitamin D deficiency results in insufficient bone mineralization and then osteomalacia.

Together with proximal tubular reabsorption of phosphate, the kidney also controls the reabsorption of calcium in the distal tubule; thus it is clear that renal dysfunction can contribute to a disruption in bone homeostasis.

The picture worsens further owing to the direct action of HIV on bone cells that is exerted both by an enhancement of osteoclastogenesis and by inhibition of osteoblast differentiation and biological activity.

Numerous and updated literature confirms these notions in HIV-1-infected people: Dao, et al. found that 71.6% of HIV-1-infected patients followed in a prospective observational cohort had insufficient levels of 25(OH)-vitamin D and this value correlated significantly with renal insufficiency (eGFR < 90 ml/min/1.73 m²) and ritonavir exposure.

In a large HIV-infected patient cohort, the prevalence of insufficient of vitamin D (< 75 nmol/l) was found in 54% of subjects, whereas deficiency was found in 7%. Race and duration of antiretroviral therapy were independent factors associated with the risk of insufficientcy of vitamin D, although the prevalence of a specific antiretroviral class was not demonstrated.

A recent French cohort study has found that 90% of treated patients had vitamin D deficiency (< 15 ng/ml) and suggested a specific role of HAART as a causative factor.
In a retrospective study on bone mineral density (BMD) of HIV-1-infected patients, measured by dual-energy X ray absorptiometry (DEXA), a progression over time to osteopenia and osteoporosis was found. Some of the factors related to low BMD were similar to those described in the general population (age, sex, low body mass index), but others were related to HIV-specific conditions: antiretroviral therapy and specifically PI and tenofovir use.

Patients treated with tenofovir showing laboratory signs of renal proximal tubular dysfunction were characterized by an imbalance in bone turnover (10% of patients presented osteoblast activation and 51% high bone resorption) that was correlated with lower eGFR, vitamin D deficiency, and hyperparathyroidism.

The association between tenofovir use and secondary hyperparathyroidism was also shown in a recent study by Pocaterra, et al. Even though the influence of the high prevalence of hypovitaminosis D on parathyroid hormone through calcium serum levels was evident, an independent effect of tenofovir use also emerged.

Regarding the correlation between renal impairment and CVD, a very large meta-analysis has shown that eGFR ≤ 60 ml/min/1.73 m² and albumin/creatinine ratio ≥ 1.1 mg/mmol were independent predictors of all causes and cardiovascular mortality risk in the general population.

In HIV-1-infected populations, similar conclusions have been drawn. A recent national longitudinal study has confirmed the association between kidney function and albumin excretion with the occurrence of atherosclerotic CVD and/or heart failure, adding that kidney function and albuminuria provide complementary prognostic information that may facilitate CVD risk stratification in HIV-infected persons.

In a case-control study, patients who had cardiovascular events (n = 63) were compared with controls (n = 252) matched by eGFR and proteinuria: an independent association between decreased kidney function and increased risk of cardiovascular events in HIV-1-infected people was demonstrated, in addition to more traditional risk factors such as history of cardiovascular events, diabetes mellitus, dyslipidemia, and low CD4+ count.

In patients of the Veterans Administration Cohort, when screened for myocardial infarction and cerebrovascular events, CKD was found to be correlated with an increased risk of myocardial infarction (HR: 3.85; 95% CI: 2.74-5.42; p < 0.0001 for eGFR < 60 ml/min/1.73 m²; HR: 1.33; 95% CI: 1.00-1.76; p = 0.048 for eGFR 60-89 ml/min/1.73 m²).

In summary, kidney function is an important regulator of bone homeostasis and is considered a cofactor in the occurrence of CVD, both in general and in HIV-1-infected populations. Monitoring renal function parameters is an important component of the overall treatment of HIV-1 infection.

**Antiretroviral drugs and renal toxicity**

The global effects of HAART on renal function and the incidence of chronic renal disease among HIV-infected patients are debated still today.

Positive effects of HAART on kidney function have been demonstrated in several cohort studies. In fact, the introduction of new antiretroviral regimens and the persistent viral suppression correlated with a declining incidence of CKD and a significant improvement in eGFR.

However, HAART itself can cause renal toxic effects, and prolonged used of antiretroviral drugs in HIV-infected patients may lead to the development of kidney dysfunction by several pathogenetic mechanisms.

The following paragraphs describe the rates and mechanisms of common toxic renal effects associated with different classes of antiretroviral agents.

**Protease inhibitors**

Indinavir is the protease inhibitor (PI) that has been most commonly associated with renal toxic effects, including nephrolithiasis, intratubular drug deposition, crystalluria, dysuria, hematuria, renal colic, papillary necrosis, renal atrophy, acute interstitial nephritis, and acute and chronic renal failure. Symptoms may occur as early as one week following initiation of indinavir therapy and urinary crystals composed of indinavir may form in any structure of the kidney and the urinary tract. Crystalluria was reported in about 20% of all patients treated with this PI, and this condition progressed to nephrolithiasis in 3% of all subjects.

Retrospective and prospective studies demonstrated that the incidence of urological complications among indinavir-treated patients was about 8-10 cases per 100 treatment-years, and risk factors for the development of nephrolithiasis were urine pH > 6, low lean body mass level, inadequate hydration, high plasma levels of indinavir, chronic hepatitis B or C, and concomitant therapy with low-dose ritonavir or other nephrotoxic drugs. Most urologic symptoms and elevations in serum creatinine usually normalize within weeks after the discontinuation of indinavir, although...
irreversible renal toxicity and chronic renal failure were described\textsuperscript{62,63}.

Several case reports of nephrolithiasis and AKI were also reported in association with full-dose ritonavir, saquinavir, nelfinavir, and lopinavir/ritonavir therapy, but the etiology of renal damage remains unclear\textsuperscript{69-72}. Observations of urolithiasis in saquinavir-treated patients are exceptional, and no renal toxicity has been attributed to saquinavir in controlled trials\textsuperscript{73}.

Atazanavir has not been associated with urolithiasis or crystalluria in clinical studies, but several cases of nephrolithiasis and interstitial nephritis were reported in atazanavir-treated patients.

In a retrospective study including 1,134 patients who were receiving ritonavir-boosted atazanavir from 2004 through 2007, only 11 cases of atazanavir-associated nephrolithiasis were diagnosed, and all cases occurred within two years after starting atazanavir treatment. Patients with low water intake, high urinary pH, and a prior history of urinary stones may have a greater risk of urine crystallization\textsuperscript{74}. Similarly, 30 cases of atazanavir-induced nephrolithiasis were recorded over a four-year study period in the Adverse Event Reporting System Database\textsuperscript{75}, but no cases of CKD were observed in these series. The mechanism of developing renal stones is unknown, but is probably linked to urinary precipitation of atazanavir, as has been described for indinavir stones. Finally, isolated cases of interstitial nephritis with acute renal failure were described in association with atazanavir or atazanavir/tenofovir therapy, but withdrawal of antiretroviral treatment resulted in recovery of renal function\textsuperscript{76}.

Thus, to date, the incidence of atazanavir-induced nephrolithiasis and interstitial nephritis appears to be very low, given that atazanavir has been administered to a very high number of patients worldwide.

Cases of nephrolithiasis were reported during post-marketing surveillance in HIV-infected patients receiving fosamprenavir. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made. If signs or symptoms of nephrolithiasis occur, temporary interruption or discontinuation of therapy may be considered\textsuperscript{77}.

**Nonnucleoside reverse transcriptase inhibitors**

Data concerning kidney toxicity from NNRTI are very limited because nevirapine, efavirenz, and etravirine have usually demonstrated a safe renal profile in controlled clinical trials.

A small number of cases of crystalluria or obstructive uropathy associated with the administration of efavirenz have been reported\textsuperscript{78,79}. Moreover, a single case report linked efavirenz to a hypersensitivity reaction including interstitial nephritis and acute renal failure. Prompt discontinuation of antiretroviral treatment and use of corticosteroids resulted in rapid recovery of renal function\textsuperscript{80}.

**Nucleoside reverse transcriptase inhibitors**

Renal toxicity associated with the use of nucleoside reverse transcriptase inhibitors (NRTI) is generally uncommon in clinical trials, but several episodes of nephrotoxicity and tubular dysfunction have been reported in subjects treated with nucleoside analogues.

Animal studies have shown that metabolic abnormalities, such as hypokalemia and hypomagnesemia, may predispose to NRTI-induced nephrotoxicity\textsuperscript{61-64}. Mitochondrial toxicity may be induced by NRTI-based therapy, particularly with stavudine, didanosine, or zidovudine. Asymptomatic hyperlactatemia following mitochondrial damage occurs in 20-30\% of HIV-infected patients receiving NRTI, and may infrequently lead to severe lactic acidosis and acute renal failure\textsuperscript{85}. Another report described acute interstitial nephritis with renal failure in association with a hypersensitivity reaction to abacavir: renal function had improved by two weeks after abacavir withdrawal\textsuperscript{86}.

**Tenofovir**

Apart from a small number of case reports of nephrotoxicity associated with PI-, efavirenz-, or NRTI-based therapy, concern over antiretroviral drug-induced renal toxicity has been largely focused on tenofovir.

The literature about tenofovir use and renal disease is non-standardized, without diagnostic specificity for the cause of renal abnormalities, and retrospective and prospective studies often produce confusion about the true incidence or prevalence of this complication. In the selected populations enrolled in clinical trials with rigorous monitoring of renal function, tenofovir appears to be associated with a low risk of nephrotoxicity and this adverse event occurs mostly in patients with predisposing kidney disease or comorbidities\textsuperscript{87-90}.

However, several case reports and various observational studies have found evidence of potential renal toxicity induced by tenofovir treatment, mostly including proximal tubulopathy with Fanconi’s syndrome and nephrogenic diabetes insipidus. Tenofovir is the
antiretroviral agent most commonly associated with Fanconi’s syndrome, which can potentially lead to calcium and phosphorus dysregulation, acute renal failure, osteomalacia, and fractures. Moreover, analyses of large datasets from tenofovir clinical trials have shown that a mild decrease in GFR may sporadically occur. Tenofovir is excreted by the kidney via a combination of glomerular filtration and active tubular secretion. On the basolateral side of the proximal tubular cell, tenofovir influx occurs primarily through the human organic anion transporter (hOAT)-1, while multidrug resistance protein (MRP)-2 and -4 are responsible for its cellular efflux. Tenofovir-associated nephrotoxicity more frequently involves the tubular function, and more interesting data result from studies investigating clinical or subclinical renal tubular toxicity. However, it is unclear whether spot proteinuria, glycosuria or urine protein/creatinine or albumin/creatinine ratio are sufficiently sensitive screening tests to detect subclinical tubular dysfunction, and other markers should be considered (such as hyperaminoaciduria, hyperphosphaturia, or hyperuricosuria), as we will see in the next section.

The incidence of CKD was investigated in the EuroSIDA Cohort Study, including 6,843 HIV-infected persons followed-up from 2004 onwards. Progression to chronic nephropathy was observed in 225 patients (3.3%) during 21,482 person-years follow-up, with an incidence of 1.05/100 person-years follow-up. After adjustment for traditional risk factors, exposure to tenofovir was significantly associated with a higher incidence of CKD, as was true for indinavir and atazanavir, whereas the results for lopinavir/ritonavir were less evident.

The same research reveals that patients treated with tenofovir, who stopped the administration of the drug, continued to have a significant increased incidence of CKD during the first year after stopping, suggesting that the effect of the drug is not easily reversible.

A cross-sectional study involving 845 HIV-infected outpatients showed a prevalence of chronic renal failure higher than that of the general population, and significant predictors of lower GFR in multivariate analyses were found to be use of tenofovir or stavudine.

In the ANRS CO3 Aquitaine Cohort, 2,613 HIV-infected patients were followed-up between 2004 and 2008 to estimate the incidence of chronic renal failure and related risk factors. The incidence rate of chronic renal failure was much higher (12.7 cases for 1,000 person-years) than that observed in the general population of similar age, and factors associated with higher incidence included immunodeficiency and tenofovir exposure.

Some other prospective cohort studies have emphasized similar results. The Swiss HIV Cohort Study found a consistent evidence for a significant reduction in GFR associated with tenofovir use. In the HIV Outpatient Study (HOPS), use of tenofovir-containing HAART was associated with modest decreases in GFR during the first year of therapy, but clinically significant renal toxicity was very uncommon, and decline in GFR in subjects with preexisting renal dysfunction was also very limited.

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In a cross-sectional study including 99 HIV-infected patients with serum creatinine levels < 1.7 mg/dl and dipstick-negative proteinuria, subjects using tenofovir had increased urine retinol-binding protein/creatinine ratio and protein/creatinine ratio, showing a subclinical renal tubulopathy. A cross-sectional study of plasma and 24-hour urine markers of tubulopathy (glycosuria, hyperaminoaciduria, hyperphosphaturia, hyperuricosuria, and beta2-microglobulinuria) in 284 HIV-positive patients demonstrated a significant correlation between
higher risk of CKD in tenofovir-treated individuals. A 48-week follow-up, no difference in eGFR was observed between the arms, but markers of tubular damage (urinary excretion of retinol-binding protein and beta2-microglobulin) increased significantly in the tenofovir/entecitabine group. Predictors of kidney tubular dysfunction in patients treated with tenofovir were also investigated. Increased age, lower body weight, higher tenofovir plasma levels, and concomitant use of didanosine, amprenavir, or ritonavir-boosted PI were found to be associated with a higher risk of CKD in tenofovir-treated individuals. Coadministration of tenofovir increases plasma concentration of didanosine by 40-60%, possibly via pharmacokinetic competition for hOAT-1 in the proximal tubular cells, increasing the risk of nephrotoxic effects.

Polymorphisms in genes associated with kidney cellular transporters could explain different toxic effects of and therapeutic responses to antiretroviral drugs. A pharmacogenetic study assessing 115 HIV-infected patients receiving tenofovir-containing HAART showed an increased risk of kidney tubulopathy among those with genotype CC than among those with genotypes CT and TT at position –24 of ABCC2 gene encoding the cellular transporter MRP2. Similarly, mutational screening of 30 HIV-positive patients has demonstrated a significant allelic association between the single-nucleotide polymorphism G→A of the ABCC2 gene and tenofovir-induced proximal tubulopathy.

On the contrary, results from clinical trials have shown no evidence of renal toxicity when tenofovir is used as part of an initial antiretroviral regimen. Gallant, et al. evaluated 432 antiretroviral-naive patients who initiated either tenofovir or any alternative NRTI after January 2002. Patients taking both tenofovir and NRTI experienced an initial decline in GFR during the first six months of therapy, but renal function stabilized between six and 24 months. By multivariate analysis, there was no difference between the tenofovir and NRTI groups in 25 or 50% decline in GFR, while subjects taking tenofovir and boosted PI had a greater median decline in GFR than those taking tenofovir and a NNRTI. However, in a previous report of the Johns Hopkins Cohort, use of tenofovir was found to be associated with a greater decline in renal function than use of alternative nucleoside analogues.

In conclusion, although clinically evident nephrotoxicity induced by tenofovir occurs only sporadically, several data indicate a significant negative impact on the proximal tubule, also in terms of progression of damage. Moreover, its potential long-term effects on kidney function are still unknown. Therefore, long-term monitoring of renal function and markers of tubular dysfunction should be considered in patients taking tenofovir, particularly those with comorbidities (such as preexisting renal disease, hypertension, and diabetes) or predisposing factors (including increased age and current therapy with boosted PI or other nephrotoxic drugs).

Other antiretroviral drugs

In the safety analysis of the TORO-1 and TORO-2 trials, including over 600 subjects treated with enfuvirtide, one patient with a previous history of proteinuria and hematuria exhibited a hypersensitivity reaction with a membranoproliferative glomerulonephritis.

No evidence exists that fusion inhibitors (enfuvirtide), CCR5-receptor antagonists (maraviroc), or integrase inhibitors (raltegravir) have potential nephrotoxic effects. Although available data are still limited, these drugs have usually shown a good renal safety profile in clinical studies. Further enlarged studies are requested in order to better investigate the potential nephrotoxic effects of new antiretroviral compounds.

Dose changes recommended in patients with renal insufficiency are summarized in table 2.

Markers

Glomerular function evaluation

Creatinine clearance measuring methods

Evaluation of serum creatinine is the most used marker in clinical practice in order to estimate renal function, but it is not an exact predictor of GFR as the levels of creatinine are influenced by several other factors such as muscular mass, age, sex, race, use of steroids, and diet. When considering methods, one can list accuracy and precision on one side and costs and feasibility on the other. Serum creatinine is obviously the simplest and most economical test, but is less precise and specific. At the opposite (maximum accuracy, less feasibility) there is the renal clearance of inulin or EDTA. Creatinine clearance measured on timely collected urine is an indirect assessment of GFR and is often affected by the imprecision in the collection.
process. To overcome these difficulties, eGFR is a valid alternative, which needs only serum creatinine measurement and some anthropometric parameters. Both the modification of diet in renal disease (MDRD) and Cockroft-Gault formulas (placed between the two extremes of accuracy and simplicity) represent a good compromise in daily clinical practice for follow-up of the kidney function. Table 2. Summary of dose reductions for antiretrovirals in patients with renal failure

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Recommended daily dosing in patients with renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Abacavir</td>
<td>No adaptation; no data for end-stage renal disease</td>
</tr>
<tr>
<td></td>
<td>Didanosine</td>
<td>Weight &lt; 60 kg ≥ 60 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 30-59 ml/min: 125 mg 200 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 10-29 ml/min: 125 mg 125 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 10 ml/min: 75 mg* 125 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD, CAPD: 75 mg* 125 mg</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine</td>
<td>CrCl 30-49 ml/min: 200 mg/48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 15-29 ml/min: 200 mg/72 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 15 ml/min or HD: 200 mg/96 hours (take dose after HD session on dialysis days)</td>
</tr>
<tr>
<td></td>
<td>Lamivudine</td>
<td>CrCl 30-49 ml/min: 150 mg/24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 15-29 ml/min: 1 x 150 mg, then 100 mg/24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 5-14 ml/min: 1 x 150 mg, then 50 mg/24 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 5 ml/min or HD: 1 x 50 mg, then 25 mg/24 hours (take dose after HD session on dialysis days)</td>
</tr>
<tr>
<td></td>
<td>Stavudine</td>
<td>Weight &lt; 60 Kg ≥ 60 Kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 26-50 ml/min: 15 mg/12 hours 20 mg/12 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 10-25 ml/min or HD: 15 mg/24 hours 20 mg/24 hours (take dose after HD session on dialysis day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 10 ml/min (not on HD): no data</td>
</tr>
<tr>
<td></td>
<td>Tenofovir</td>
<td>CrCl 30-49 ml/min: 300 mg/48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl 10-29 ml/min: 300 mg twice a week</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 10 ml/min not on HD: no data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HD: 300 mg once a week (take dose after HD session on dialysis days)</td>
</tr>
<tr>
<td></td>
<td>Zidovudine</td>
<td>CrCl 30-49 ml/min: 1 tablet/48 hours</td>
</tr>
<tr>
<td></td>
<td>Emtricitabine + tenofovir (co-formulated)</td>
<td>CrCl 30-49 ml/min: 1 tablet/48 hours</td>
</tr>
<tr>
<td></td>
<td>NNRTI</td>
<td>Efavirenz, etravirine, nevirapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No adaptation</td>
</tr>
<tr>
<td></td>
<td>Pro tease inhibitors</td>
<td>Darunavir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl ≥ 30 ml/min: no adaptation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 30 ml/min: no data</td>
</tr>
<tr>
<td></td>
<td>Lopinavir, saquinavir</td>
<td>No adaptation</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir, indinavir, nelfinavir</td>
<td>No data</td>
</tr>
<tr>
<td></td>
<td>Entry inhibitors</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No adaptation</td>
</tr>
<tr>
<td></td>
<td>Maraviroc</td>
<td>CrCl &lt; 80 ml/min: without a concomitant potent CYP3A inhibitor or inducer: no adaptation with a concomitant potent CYP3A inhibitor or inducer: 150 mg/24 hours with fosamprenavir: 150 mg/12 hours</td>
</tr>
<tr>
<td></td>
<td>Integrase inhibitors</td>
<td>Raltegravir</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No adaptation</td>
</tr>
</tbody>
</table>

* Oral solution.
NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: nonnucleoside reverse transcriptase inhibitors; CrCl: creatinine clearance; HD: hemodialysis; CAPD: continuous ambulatory peritoneal dialysis.
CKD-EPI formula to assess eGFR has a better performance than MDRD, especially in the near-normal renal function; however, in order to apply such a formula, serum creatinine levels need to be measured by a laboratory method that uses a reference-standardized creatinine calibrator, not readily available in all clinical chemistry laboratories.

**Cystatin C**

Another marker of glomerular function is cystatin C, produced constantly by almost all the cells, filtered completely by the glomerulus and then reabsorbed and catabolized by renal tubules. A study on HIV-related kidney diseases evidenced that serum cystatin C was higher in 1,008 HIV-positive patients than in HIV-negative subjects, even if all subjects showed similar values of serum creatinine.

Serum cystatin C concentrations are affected by several factors such as sex, age, and race; but, differently from creatinine, it does not seem to be influenced by muscle mass. The persistent inflammatory state seen in HIV-infected patients may contribute to increase mean levels of cystatin C in these patients. This is another confounding factor limiting its use as GFR marker in this particular group of patients.

**Evaluation of tubular function**

**Serum/urine phosphorus concentration**

HIV-infected patients seem to have additional causes of low serum phosphorus concentration compared with the general population, such as:

- Hypovitaminosis D: in literature there is a great evidence of this condition related to HIV status. Several factors have accounted for this such as the in vitro demonstrated effect of reduction of the 25- and 1- hydroxylation by protease inhibitors; in literature a role of efavirenz has been proposed as well.
- Toxicity on proximal tubule by HAART or HIV itself.

Monitoring of phosphorus metabolism is mandatory in this group of patients; besides vitamin D, other factors that need surveillance are parathyroid hormone and bone alkaline phosphatase. Moderate increased levels of parathyroid hormone are associated with vitamin D insufficiency or deficiency. Probably, an early event is represented by the increased urinary phosphate excretion that needs an accurate evaluation, better if correlated to GFR (TmPO4/GFR) according to the nomogram of Walton and Bijvoet.

**Proteinuria, uricosuria, and glycosuria**

These are all markers of tubular damage. In the study of Hall, et al., several markers of subclinical damage were analyzed; however, it remains unclear if spot urines are reliable specimens in order to estimate subclinical tubular damage. Generally, the examination of 24-hour collected urine is required. In the guidelines for the screening of CKD in HIV of the National Kidney Foundation, several methods of measurement of proteinuria are compared: dipstick (semiquantitative method); proteinuria on spot urines (quantitative), preferentially collected in the morning, with calculation of urinary protein/creatinine and albumin/creatinine ratios; proteinuria in 24-hour collected urines (gold standard, but potentially influenced by mistakes in collection and consequent under/overestimation).

The Infectious Diseases Society of America (IDSA) guidelines suggest the use of dipstick for the estimate of proteinuria. Such method has a sensitivity of approximately 60% and a positive result must be confirmed measuring the protein/creatinine ratio or albumin/creatinine ratio on randomly sampled urine (better if collected in the morning).

It is important to calculate both total urinary protein and albumin ratios in order to discriminate between glomerular proteinuria and tubular proteinuria. In some clinical conditions, no direct correlation exists between 24-hour proteinuria and protein/creatinine ratio on spot urine samples. Therefore, estimation of total protein in timely collected urine samples is the method of choice. Assessing protein and creatinine on near-24-hour urine samples can offset error in urine collection.

Normoglycemic glycosuria is another element that suggests the presence of proximal tubular damage. Moreover, since uric acid is highly reabsorbed at this nephron level, with a fractional excretion that usually does not exceed 10% of the filtered uric acid, an increase in urinary uric acid excretion is an early marker of proximal tubular dysfunction.

**Microalbuminuria**

Chronic kidney disease and overt proteinuria have been associated with adverse outcomes in HIV-infected patients. Lower levels of urinary albumin excretion,
or microalbuminuria, have also been associated with increased mortality in diabetics\textsuperscript{132}. Several studies have demonstrated an increased prevalence of microalbuminuria in HIV-infected individuals both before\textsuperscript{133} and after the introduction of HAART\textsuperscript{26,27}. A recent study identified a graded relationship between the degree of microalbuminuria and the risk of mortality\textsuperscript{134}. The detection of proteinuria or microalbuminuria on a single urine specimen was associated with an increased risk of mortality, even after adjustment for markers of HIV disease severity. The data suggest that microalbuminuria testing may prove useful as prognostic information in HIV-infected individuals.

**Beta 2 microglobinuria**

Beta 2 microglobinuria (B2M) is a specific marker of tubular damage.

In a paper by Soriano, et al., urinary B2M excretion was particularly high in a group of HIV-infected patients receiving tenofovir-including HAART, but it turned out to be elevated, even if at lower levels when compared to the above group, also in HIV-infected patients with a detectable viremia as to suggest a role in the tubular damage of HIV itself. Beta 2 microglobinuria was within a normal range in patients with suppressed viremia not receiving tenofovir-including HAART\textsuperscript{99}.

In a small case series, increased urinary excretion of B2M was reported after 12 weeks in a group of tenofovir-treated patients in comparison with other antiretroviral-treated patients. Interestingly, the fractional reabsorption of phosphate decreased progressively from 12 to 24 weeks, suggesting that B2M excretion could be interpreted as an early marker of tubular dysfunction, manifested later on with an increased urinary loss of phosphate\textsuperscript{135}.

In larger studies, urinary B2M levels were elevated in a higher proportion of tenofovir-treated patients compared with non-tenofovir-treated patients. Serum creatinine and creatinine clearance or eGFR did not differ significantly in the two groups\textsuperscript{136}.

Measurement of urinary B2M, however, presents some troubles due to the easy degradation of the molecule at low pH; therefore, this marker has lost its utility in the evaluation of tubular dysfunction in general.

**N-acetyl-beta-D-glucosaminidase**

N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme contained in the proximal tubular cells and has been used as a marker of cell damage and tubular dysfunction. NAG enzymuria is increased in both tenofovir-containing HAART and non-tenofovir HAART compared to naive patients\textsuperscript{98}.

**Retinol binding protein**

Retinol binding protein (RBP) is low molecular weight protein completely filtered by the glomerulus and reabsorbed by the proximal tubule. Its presence in urine is an indirect index of tubular damage. High values of urinary excretion of RBP have been found in patients treated with tenofovir-containing HAART\textsuperscript{98,101}.

**Novel markers**

**Neutrophil gelatin-associated lipocalin**

Neutrophil gelatin-associated lipocalin (NGAL) is supposed to be an early and sensitive marker of acute renal damage\textsuperscript{128}. Although this marker has been studied extensively in different clinical settings, such as sepsis, cardiopulmonary bypass, multiple organ failure, renal drug toxicity, and acute rejection, in HIV-infected patients, NGAL has been only studied in pediatric patients. This study showed a progressive reduction of NGAL in children with demonstrated HIVAN at the renal biopsy compared to the beginning of HAART\textsuperscript{137}. However, it is not clear if such decrease is due to the improvement of the cellular immunity related to HAART or just to the recovery of kidney function.

**Asymmetric dimethylarginine**

Asymmetric dimethylarginine (ADMA) is an inhibitor of nitric oxide synthetase and reflects the endothelial function. In HIV-negative patients with kidney disease, this marker has been associated to a faster progression to dialysis\textsuperscript{138}.

**Liver-type fatty acid binding protein**

Liver-type fatty acid binding protein (L-FABP) is a marker of integrity of the proximal tubule. In a study on 120 patients with CKD, without diabetes and without HIV infection, this marker has not turned out to be related to elevated levels of proteinuria and creatininemia\textsuperscript{139}.

In the literature, no studies have analyzed the role of these markers in HIV-infected patients, particularly the last two ones.

Accordingly with what so far discussed, we propose a practical algorithm that nicely fits with our clinical
experience in the management of kidney disease during HIV infection (Fig. 2).

The future of the renal damage

With the advent of HAART, physicians facing HIV infection have been forced to switch their attention from the control of viral load and immunological state toward a deeper comprehension and management of comorbidities\textsuperscript{140}. In fact, HIV and HAART can harm many organs and tissues and undoubtedly kidneys are main targets. The onset of HIVAN is well described, but, fortunately, it is also quite rare\textsuperscript{24}. Many other alterations of renal function have been growing during the years. As discussed in other sections of this review, the counterpart of the reduction of AIDS-related deaths

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*Figure 2. A practical approach to kidney disease in HIV-1 patients.*
has been the increased mortality for renal and cardiovascular diseases, and this has defined, also in HIV-positive populations, a close correlation between kidneys and heart. Many data confirm that a reduction of GFR is strictly correlated with increased CVD, both in the general population and in HIV-positive subjects. In addition to traditional risk factors known to reduce GFR (such as aging, race, diabetes, hypertension), many infection-related conditions can exacerbate cardiovascular risk: use of tenofovir and PI, co-infection with HBV, opportunistic infections, low CD4+ nadir, high plasma HIV-RNA. Alterations in GFR can also cause bone derangement. Dialysis patients frequently show a bone disease called renal osteodystrophy, but also slighter reductions of GFR can negatively affect bone health, by increasing parathyroid hormone production and osteoclast activity and by reducing the activation of vitamin D. A growing body of evidence demonstrates that these alterations of mineral metabolism can increase CVD. In patients with osteoporotic fractures, the hazard ratios for stroke and first cardiovascular event are 4.1 and 4.7, respectively.

All these considerations seem to close the circle. Kidneys, heart, and bone share common risk factors that can damage all these organs and tissues. Due to its central role, GFR could be regarded as one of the trait d’union between these apparently different diseases.

Patient’s perspective

Renal complications are common among people living with HIV: in fact, up to 30% of HIV-positive individuals may have protein in their urine, a sign of kidney dysfunction. It is difficult to estimate accurately how many people develop kidney disease and, therefore, to implement effective disease prevention or early intervention because kidney dysfunction may be asymptomatic or may result in only vague symptoms such as fatigue or general malaise. Without specific symptoms, many individuals are diagnosed later in their disease course, reducing the efficacy of available treatments.

Given the risks associated with kidney disease, developing awareness of kidney function and getting the necessary tests are essential to maintaining good health with HIV.

Our knowledge that HIV affects the kidneys is solid, but our understanding of certain areas of renal health is still rudimentary. Significant work remains to truly elucidate who is susceptible to kidney disease and why, and how to treat certain kidney diseases that occur in HIV-positive people.

Early screening for kidney disease provides a greater likelihood of effective prevention and treatment. Screening and risk assessment are as simple as a urine analysis for protein, blood test for serum creatinine, and simple formulas for specific evaluations. They should be performed in every person living with HIV: the Italian Guidelines on the HIV-1 therapy and management of people living with HIV/AIDS currently strongly recommends that all HIV-positive people should be screened for kidney disease at least once a year, and those with abnormal screening tests should receive further evaluation by their HIV physician and see, when necessary, a nephrologist.

Key to this recommendation is awareness of kidney disease. Without awareness in both the HIV-positive community and among HIV physicians, potentially preventable and treatable problems can progress unchecked in the unsuspecting and asymptomatic individual. Awareness can lead to a very simple, but potentially life-saving: question: “Hey doc, are my kidneys OK?”

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