

HAART-related nephropathies in HIV-infected patients

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HAART-related nephropathies in HIV-infected patients. There is no doubt that highly active antiretroviral therapy (HAART) has been the most important progress in the therapy of human immunodeficiency virus (HIV)-infected patients in the last decade. A growing number of observations suggest that the beneficial effects of HAART also include improvement of HIV-related renal complications. Consequently, the cohort of HIV-infected patients requiring HAART has increased and includes patients with preexisting nephropathies, whether related or unrelated to HIV infection. However, some antiretroviral drugs may have renal- and life-threatening side-effects, especially if underlying renal abnormalities exist. In this review, we focus on those aspects that require particular attention in preventing new health complications in HIV-infected patients.

Current guidelines for treatment of human immunodeficiency virus (HIV) infection recommend the combination of three antiretroviral agents, two reverse transcriptase inhibitors (RTI) plus one protease inhibitor, or the association of three RTIs [1, 2]. These regimens of highly active antiretroviral therapy (HAART) have dramatically reduced the morbidity and mortality of HIV infection.

Nephropathies in HIV-1-infected patients have been recognized for two decades [3, 4]. They consist mostly of glomerular nephropathies, but also of vascular or tubulointerstitial nephropathies [5]. Recently, a growing volume of virologic and histologic evidence suggests that HIV-associated nephropathy (HIVAN), the most usual form of HIV-1-related nephropathy, may be the consequence of HIV-1 replication in the kidney. The possible relation of HIVAN with HIV-1 replication in the kidney correlates with epidemiologic and clinical data showing that HAART may improve HIVAN.

However, from a nephrologist's point of view, one consequence of this success has been the emergence of new kidney diseases related to (1) a better control of the HIV infection and (2) the potential nephrotoxicity of antiretroviral therapies. Here we summarize the reported renal adverse effects of the antiretroviral drugs and give some insights into their pathophysiology. We try as well to delineate a new characterization of kidney diseases in HIV-1-infected patients since the beginning of the HAART era. This new profile has been linked to better control of HIV infection and to the potential nephrotoxicity of some antiretroviral treatments.

HIVAN

The most common HIV-1-related nephropathy is HIVAN, a focal segmental glomerulosclerosis (FSGS) associated with severe cystic tubular lesions, leading to chronic renal failure, especially in its collapsing variant [6]. HIVAN usually affects black patients, and is known to be a leading cause of end-stage renal disease (ESRD) in this population in North America and in Europe [7–11]. During the last 5 years, significant advances in the pathophysiology of HIVAN have been achieved. Data from animal models and from human renal biopsies tend to point to HIV-1 infection of renal tubular cells and podocytes as being responsible for the lesions observed in HIVAN (for review, see [11]). Moreover, the recent demonstration that renal tubular cells in patients with HIVAN constitute a viral reservoir where active replication of HIV-1 is independent of that in peripheral blood mononuclear cells strengthens the hypothesis of a direct role of HIV-1 in HIVAN pathogenesis [12]. The HIV-1-encoded protein *Nef* seems to be an important candidate for HIV-1 nephrotoxicity since *Nef* is capable of inducing podocyte abnormalities in vitro similar to those observed in HIVAN [13]. Nonetheless, the efficacy of antiretroviral therapy on the course of HIVAN (see below) does not constitute a solid argument for a direct role of HIV-1 in HIVAN as it might well also be related to its indirect effect on systemic HIV-1 replication. In addition, it is not clear if the renal reservoir of HIV-1 thought to be implicated in HIVAN is affected by HAART or not [12].

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THE BENEFITS OF HAART

In the pre-HAART era, HIVAN was considered to have a poor prognosis. In addition to the antiretroviral therapy, two types of treatment were proposed to improve the course of HIVAN: prednisone and angiotensin-converting enzyme (ACE) inhibitors. Only one limited prospective study [14] and several retrospective studies [15–18] argue for the use of both corticosteroids and ACE inhibitors in HIVAN. In most studies, however, therapeutic results of ACE inhibitors and prednisone were poor, especially when considering the infectious side-effects of the latter. Antiretroviral therapy such as zidovudine was considered of interest in delaying but not in preventing ESRD [19–21]. Nonetheless, in the pre-HAART era these reports supported the idea that anti-HIV therapies could be relevant in the therapeutic strategy of HIV-1-related nephropathies [17, 19–21].

Since the onset of HAART, national epidemiologic data show the reduction of incidence of ESRD due to HIV-associated renal disease in the United States [5, 22]. This suggests that antiretroviral therapy may prevent HIVAN or at least slow its course. Preliminary retrospective series or case reports support the efficacy of HAART in improving outcome in HIVAN [16, 23–27]. In 1998, Wali et al [23] reported a 37-year-old HIV-1-positive African American man with HIVAN requiring hemodialysis. A few months after the beginning of HAART, dialysis was stopped, creatinine and proteinuria improved, and histologic lesions recovered. A similar benefit of HAART is reported by Kirchner [27] in two African American patients with suspected HIVAN and in one patient with biopsy-proven HIVAN who exhibited marked improvement in renal function after treatment with two nucleoside RTIs and one antiprotease. In a retrospective cohort study, Szczech et al [16] reviewed 19 patients with HIVAN or other HIV-1-related renal diseases, leading to ESRD in seven. Treatment with protease inhibitors (and prednisone) was associated with a slower decline in renal function. Cosgrove, Abu-Alfa, and Perazella [26] reported another retrospective series of 23 patients with HIV-1-related nephropathies, including patients with HIVAN. Thirteen patients, counting those with HIVAN, were treated with HAART and none doubled their serum creatinine. In the non-HAART group, all patients manifested a doubling of serum creatinine, two patients died, and eight required dialysis. One study [abstract; Burckle C et al, *J Am Soc Nephrol* 13:381A, 2002] retrospectively comparing two cohorts of 102 and 33 patients with biopsy-proven-HIVAN in the pre-HAART and in the HAART era, respectively, also argues for improvement of renal survival by HAART. However, the lack of definitive histologic diagnosis of HIVAN in some of these patients, the absence of controls, the small number of patients and the retrospective design of the studies did not allow firm conclusions to be drawn. Nonetheless, despite

the lack of definitive evidence due to the limited true database for HAART efficacy in renal disease, we speculate that combination antiretroviral therapy constitutes the most important therapeutic progress in preventing ESRD in HIV-related nephropathies since the beginning of the HIV epidemic. The idea of prospective controlled trials evaluating HAART on HIVAN or other HIV-1-related nephropathies is not ethically defensible, considering that the clear benefit of HAART on the survival of HIV-infected patients does not allow the design of a placebo-controlled group.

RENAL SIDE-EFFECTS OF ANTIRETROVIRAL MEDICATIONS

The growing population of patients treated with HAART and the predicted larger use of these regimens in patients with previous HIV- or non-HIV-related nephropathies requires the consideration of the potential renal side-effects of antiretroviral treatments. We list below the anti-HIV drugs recognized or reported as potential inducers of renal complications (summarized in Table 1). Some renal abnormalities are only case-reported and concern patients receiving multiple treatments; therefore, their relation with an antiretroviral drug is unclear. The renal toxicity of nonantiretroviral drugs used in HIV patients, such as aminoglycosides, amphotericin B, cidofovir, foscarnet, or pentamidine will not be detailed here.

Protease inhibitors

Indinavir. Among protease inhibitors, indinavir is the most frequently associated with renal or urologic side-effects: reversible acute renal failure, chronic renal failure, leukocyturia, microhematuria, mild proteinuria, nephrolithiasis, papillary necrosis, and crystalluria (Table 1). Symptoms may occur as early as 1 week following initiation of indinavir therapy [28]. They are related to the crystallization of indinavir that can occur in all anatomic structures from the proximal tubules to the bladder. Infrared spectrophotometry, mass spectrometry and high-performance liquid chromatography (HPLC) studies have confirmed that these crystals are composed of indinavir [28, 29]. Risk factors are urine pH above 6, high dose of indinavir, besides the usual risk factors for nephrolithiasis (dehydration, warm environmental temperature, etc.) [29–33]. Cotreatment with trimethoprim-sulphamethoxazole or aciclovir may also constitute a risk factor for renal or urinary indinavir-related adverse events [34, 35]. Moreover, side-effects related to indinavir crystallization may be synergized by renal hemodynamic dysregulation, since indinavir reduces glomerular filtration rate (GFR) and renal blood flow (RBF) in rats [36].

The prevalence and incidence of indinavir-related urinary and renal side-effects have been variably estimated.

Table 1. Renal abnormalities reported in patients with antiretroviral agents used against human immunodeficiency virus (HIV) infection

Antiretroviral subfamily	Generic name/trade name	Renal abnormalities	Histology	References
Protease inhibitors	Amprenavir/Agenerase	Not reported		
	Indinavir/Crixivan	Renal colic, flank pain, dysuria, acute renal failure, chronic renal failure, leukocyturia, microhematuria, mild proteinuria, urolithiasis, papillary necrosis, crystalluria, urinary tract obstruction by radiolucent calculi, and renal parenchymal defects	Tubulointerstitial nephritis with indinavir crystals in tubules	[28, 29, 32–35, 37–47, 88–93]
	Lopinavir (plus ritonavir)/Kaletra	Not reported		
	Nelfinavir/Viracept	Renal colic		[48]
Nucleoside reverse transcriptase inhibitors	Ritonavir/Norvir	Acute renal failure		[49, 51–53]
	Saquinavir/Invirase or Fortovase	Not demonstrated		
	Abacavir/Ziagen	Acute renal failure	Acute interstitial nephritis	[81]
	Didanosine/Videx	Proximal tubular dysfunction (Fanconi's syndrome)		[77]
	Lamivudine/Epivir or Zeffix	Proximal tubular dysfunction (Fanconi's syndrome)?		[78]
	Stavudine/Zerit	Proximal tubular dysfunction (Fanconi's syndrome)?		[78]
Nucleotide reverse transcriptase inhibitors	Zalcitabine/Hivid	Not reported		
	Zidovudine (azidothymidine)/Retrovir	Not reported		
	Tenofovir disoproxil fumarate/Viread	Acute renal failure, proximal tubular dysfunction (Fanconi's syndrome), nephrogenic diabetes insipidus, nephritic syndrome, leucocyturia of apparent tubular origin	Proximal tubular cells abnormalities	[71–74]
Nonnucleoside reverse transcriptase inhibitors	Delavirdine/Rescriptor	Not reported		
	Efavirenz/Sustiva	Not reported		
HIV-1 fusion inhibitor	Nevirapine/Viramune	Not reported		
	Enfuvirtide	Membranoproliferative nephritis?		[55]

In a prospective study of 54 indinavir-naïve HIV-positive individuals by Gagnon et al [37], the prevalence of crystalluria was 67% at the beginning of treatment but decreased to 25% after 2 weeks.

The frequency of urinary complications (renal colic, flank pain) has been estimated between 7.4% and 20.8% [28, 34, 35, 38–40]. Kopp et al [28] evaluated the frequency of indinavir-related urinary tract abnormalities. Nineteen of the 240 patients (8%) receiving indinavir followed over a 26-month period developed urologic symptoms. Of these, seven (3%) had nephrolithiasis and the other 12 (5%) had crystalluria associated with dysuria or with back or flank pain (of 40 patients who were not receiving indinavir, none had similar crystals). In a study of 1219 patients, including 644 individuals treated with indinavir, Dieleman et al [41] estimated at 8.3 per 100 treatment-years the incidence of indinavir-related urologic/nephrologic symptoms (nephrolithiasis, renal colic, flank pain, hematuria, renal failure, or nephropathy) versus 0.8 per 100 treatment-years for other HIV protease inhibitors. The incidence of renal colic was prospectively estimated at 23.6% over 2 years in a cohort of 555 patients treated with a HAART regimen, including indinavir [42]. In a prospective study over 48 weeks evaluating the as-

sociation of ritonavir/indinavir, 100/800mg twice daily in a HAART regimen, 19 (33%) out of 57 patients discontinued study medication because of nephrolithiasis [43].

The frequency of mild reversible renal failure has been estimated from 9% to 25% [32–34, 37, 40]. A retrospective analysis of patients treated with indinavir by Sarcletti et al [40] identified renal failure (creatinine over 1.4 mg/dL) in 13 of 72 patients (18%). It occurred after a mean duration of indinavir treatment of 32 weeks and was preceded by and associated with leukocyturia, with variable microhematuria but not urolithiasis. For the most part, renal abnormalities were reversible within 3 months after indinavir withdrawal. However, in three out of five patients with incomplete reversal of creatinine elevation, histology revealed tubulointerstitial nephritis with crystals in collecting ducts, tubular atrophy, and interstitial fibrosis. The association between leukocyturia and renal failure has been confirmed in three prospective studies, where leukocyturia was found in 37% to 39% and increased serum creatinine in 9% to 25% of adults and children. Leukocyturia was assumed to result from the tubulointerstitial nephritis [32, 33, 37]. In these series, renal abnormalities usually reversed within 3 months after indinavir discontinuation.

Urinary and renal indinavir-related side-effects are usually reversible with indinavir withdrawal and symptomatic treatment, including relief of urinary tract obstruction if necessary [28, 32–34, 37, 40]. However, the main problem is to continue indinavir. One must balance between the antiretroviral efficacy of indinavir and the recurrence of side-effects or even definitive renal injury. Indeed, renal scarring after renal indinavir-related adverse effects was initially suggested by the report by Tashima, Horowitz, and Rosen [44] showing renal interstitial fibrosis and tubular atrophy in the renal biopsy specimen of a woman with indinavir-related acute renal failure. Several subsequent studies confirmed the possibility of permanent mild renal function decrease following indinavir nephropathy [40, 45–47]. Whatever the nature of renal or urinary complications, they are responsible for indinavir discontinuation in up to 33% of patients [43]. In case of continuation, close monitoring and preventive measures are required to avoid relapses of the renal abnormalities: enhancement of urine flow through increased fluid intake, indinavir dosage adjustment, regular urine examination, creatinine monitoring, etc.

Nelfinavir. Urinary side-effects are very rare with nelfinavir. Only the case of one patient who experienced renal colic related to a stone composed almost exclusively of nelfinavir has been reported [48].

Ritonavir. Acute renal failure has been related to ritonavir [49–53]. Increase in serum creatinine can occur as soon as 3 days after the introduction of ritonavir and may require dialysis. Renal failure is usually reversible with discontinuation of the drug. Bochet et al [53] reported renal failure in 12 out of 87 (13.8%) patients receiving ritonavir without saquinavir. Median increase in serum creatinine was 66% (51% to 242%). However in this uncontrolled study, renal manifestations were not exclusively attributable to ritonavir and no renal histology was performed.

Saquinavir. Observations of renal calculi in patients treated with saquinavir are exceptional [54], and no renal toxicity has been attributed to saquinavir in controlled trials.

HIV-1 fusion inhibitor

Enfuvirtide (or T20) is a new member of the anti-HIV arsenal. It is a 36 amino acid peptide binding to the envelope glycoprotein 41 of HIV-1 thus inhibiting the fusion of the virus and the membrane of the CD4-positive cells. In the safety analysis of the TORO 1 and TORO 2 trials, including 663 patients treated with enfuvirtide to evaluate its addition to a background antiviral treatment, one patient with previous history of proteinuria and hematuria exhibited a hypersensitivity reaction with a membranoproliferative nephritis [55]. Further trials are necessary to clearly evaluate the renal toxicity of this drug.

Nucleotide RTIs

Adefovir, a prodrug of 9-(2-phosphonylmethoxyethyl) adenine analogue of adenosine monophosphate (AMP), was the first drug of a new class of nucleotide analog inhibitors of reverse transcriptase (RT) that now includes two other drugs, cidofovir and tenofovir. They differ from nucleoside RTIs in having an acyclic monophosphate component attached to the base.

They are eliminated as unchanged drug in urine by active secretion into the proximal tubular fluid through proximal tubular cells [56]. Adefovir and cidofovir secretion is presumably dependent on a key component of the secretory pathway of organic anions, the renal organic anion transporter 1 (OAT1), a basolateral kidney exchanger allowing the uptake of organic anions [57].

Adefovir/cidofovir/tenofovir-related nephrotoxicity is now well-established and is related to tubular proximal cell toxicity responsible for Fanconi's syndrome and renal failure in these patients (Table 1).

Adefovir and cidofovir accumulate in proximal tubular cells and their *in vitro* cytotoxicity is proportional to cellular OAT1 expression [57]. Moreover, *in vitro* inhibition of OAT1 by probenecid or nonsteroidal anti-inflammatory drugs (NSAIDs) reduces adefovir/cidofovir intracellular accumulation and cytotoxicity, strongly suggesting a direct cytotoxic effect of adefovir/cidofovir intracellular accumulation [58]. However, the beneficial effects of long-term coadministration of NSAIDs or probenecid that may protect the nephrons by inhibiting proximal tubular cell uptake of adefovir/cidofovir has not been clearly demonstrated. In addition, it would be probably diminished by the nephrotoxicity these drugs themselves possess.

Adefovir is currently not approved by the federal Food and Drug Administration (FDA) in the United States and drug agencies from other countries for treatment of HIV infection, due to concerns regarding serious adverse effects. However, the description of adefovir renal side-effects is highly instructive in the understanding of nephrotoxicity of nucleotide RTIs. Hence, we will report renal side-effects of adefovir in addition to those of tenofovir, the sole nucleotide RTI used in HIV infection treatment. Cidofovir is mainly used for cytomegalovirus (CMV) infection treatment but it has a dose-dependent renal toxicity (renal tubular toxicity responsible for Fanconi's syndrome and mild to severe renal failure) that could contribute to the renal morbidity of HIV-infected patients [59–63].

Adefovir. In a randomized controlled trial [64], 120 mg/day adefovir nephrotoxicity occurred in up to 61% of patients after 72 weeks. Renal failure did not resolve within 24 weeks after adefovir discontinuation in 12% of these patients. Reducing daily dosage of adefovir to 60 mg/day did not significantly reduce the occurrence of renal side-effects and did not improve the reversibility

of adefovir nephrotoxicity [65]. Similar conclusions followed the ADHOC trial [66] and were reported by other studies [67]. Nonetheless, two recent controlled trials successfully evaluating adefovir for the treatment of hepatitis B have confirmed that the nephrotoxicity of adefovir is dose-dependent, less frequent with lower dosages (30 mg/day), and is reversible with dose reduction or interruption of the treatment [68, 69].

The report by Tanji et al [70] provides some important clues about the mechanisms of adefovir toxicity. They reported a patient receiving 60 mg/day adefovir, hydroxyurea, stavudine, and indinavir with acute renal failure and proximal tubular dysfunction. These renal abnormalities were attributed to adefovir nephrotoxicity through an induced renal mitochondrial cytopathy. The authors observed tubular degenerative changes of proximal tubules with swollen and dysmorphic mitochondria on histologic and ultrastructural examination. In tubular cells, respiratory chain components encoded by mitochondrial DNA (cytochrome oxidase subunit I) were selectively deficient in renal tubular cells and mitochondrial DNA was quantitatively reduced.

Tenofovir. Tenofovir disoproxil fumarate is the most recent nucleotide reverse transcriptase inhibitor. As with adefovir, renal toxicity of tenofovir has been reported. The tenofovir-related renal abnormalities appear to be basically similar to those observed with adefovir suggesting a similar physiopathology. They consist of acute renal failure with proximal tubular dysfunction [71–74]. Nevertheless, some differences from adefovir-related lesions are noted. In the case reported by Verhelst et al [71], renal abnormalities, that were reversible with tenofovir withdrawal, included a nephrogenic diabetes insipidus attesting to collecting duct injury even though renal histology demonstrated mainly proximal tubular cell abnormalities. Creput et al [73] observed a patient who abruptly developed an acute nephritic syndrome with acute renal failure, Fanconi's syndrome, and leukocyturia of apparently tubular origin. Renal biopsy revealed proximal tubular necrosis and proximal tubular cells with thin and vacuolated cytoplasm and nuclear abnormalities suggesting viral inclusions. There was mild peritubular inflammation but, surprisingly no glomerular nor vascular changes. Two months after tenofovir discontinuation, creatinine had not returned to its baseline level.

However, renal toxicity of tenofovir is much less frequent than that observed with adefovir. In the phase I/II trial, 49 patients were randomly assigned to receive daily 75 mg, 150 mg, 300 mg, or 600 mg tenofovir or placebo. As of 28 days no renal abnormalities could be attributed to tenofovir [75]. In a phase II randomized double-blind placebo-controlled multicenter trial, 181 patients were assigned to add 75 mg, 150 mg, or 300 mg tenofovir or placebo to their background therapy. Safety assessments included the effects of tenofovir on renal parameters. Af-

ter 48 weeks no renal abnormalities were observed, particularly no significant creatinine elevation as well as no differences in changes in phosphorus levels, nor in the incidence of proteinuria between adefovir and placebo groups [76].

Nucleoside RTIs

Nucleoside RTIs renal toxicity is less frequent than that of nucleotide RTIs. Two types of renal injuries have been observed. First, nucleoside RTIs renal toxicity may involve the proximal tubule similarly to nucleotide RTIs. One case implicated didanosine [77] and one case implicated lamivudine and/or stavudine [78]. Second, acute renal failure may occur in patients with lactic acidosis secondary to nucleoside RTI-related acquired mitochondrial cytopathy [70, 79, 80]. However, it is unclear whether renal failure corresponds to an indirect mechanism observed in patients with multiorgan failure requiring intensive care, or is the result of a mitochondrial cytopathy directly affecting the kidney (see below). In addition, one publication reports a renal biopsy-documented acute immunoallergic interstitial nephritis related to abacavir in a patient experiencing acute renal failure. Renal function had improved by 2 weeks after abacavir withdrawal and initiation of a course of corticosteroids [81].

MECHANISMS OF RTIs TUBULAR TOXICITY: THE MITOCHONDRIAL CYTOPATHY HYPOTHESIS

RTIs are nucleoside or nucleotide analogs that impede HIV replication through HIV reverse transcriptase inhibition. Although the selectivity of RTIs for HIV reverse transcriptase is important, they can also inhibit DNA polymerase from the host cell and may affect nuclear or mitochondrial DNA. DNA polymerase γ implicated in the mitochondrial DNA (mtDNA) replication is targeted by RTIs with subsequent mtDNA deletions and secondary deficits in mtDNA-encoded enzymes of the mitochondrial respiratory chain. Oxidative phosphorylation is impaired in mitochondria with deficits in energy production (ATP), intracellular lipid accumulation upstream of the Krebs cycle and oxidative phosphorylation, and with production of lactate from anaerobic respiration. At the clinical level, the mitochondrial deficiency is responsible for adverse effects such as life-threatening lactic acidosis, myopathy, cardiomyopathy, peripheral neuropathy, pancreatitis, hepatic steatosis, and possibly fat redistribution syndrome grouped under the entity of RTI-induced mitochondrial cytopathy [80, 82, 83].

Therefore, it is tempting to speculate that the tubular toxicity of nucleoside or nucleotide RTI is related to, or augmented by, renal localization of an acquired antiretroviral-related mitochondrial cytopathy. Several

features of RTI renal toxicity argue in favor of such an hypothesis.

First, among recognized adverse-effects of RTIs, mitochondrial toxicity as well as renal toxicity are induced by all the members of the RTI family [1, 80]. To a greater or lesser degree, all are responsible for proximal tubular cell toxicity that clinically manifests as proximal tubular dysfunction (Table 1). Therefore, it is tempting to make a link between the tubular cell toxicity and the mitochondrial toxicity of RTI.

Second, HAART-treated patients often present with renal failure clinically and histologically related to tubulointerstitial nephropathy and associated with extrarenal manifestations attributable to mitochondrial cytopathy (personal observations).

Third, intracellular droplets, likely lipid, are present in proximal tubular cells of patients with renal toxicity of tenofovir or adefovir [71, 73]. It is well established that intracytoplasmic lipid droplets are a characteristic of unused fatty acids in cells with defective mitochondria [80].

Finally, the mitochondrial cytopathy hypothesis was invoked to explain adefovir and/or stavudine nephrotoxicity by Tanji et al [70] (Table 1) who reported in 2001 a patient with degenerative changes in proximal tubules and renal tubular cells with dysmorphic mitochondria, deficiency of the mtDNA-encoded respiratory chain and mitochondrial DNA depletion.

The demonstration of such a mechanism has potential clinical implications in preventing renal toxicity of RTIs. Moreover, it could help physicians to track down mitochondrial cytopathy at an early stage with only renal expression, and thus prevent extrarenal morbidity or mortality through lactic acidosis. In this context, measuring the renal impact of RTI-induced mitochondrial cytopathy is necessary. RTIs being a cornerstone family of drugs essential to the treatment of HIV-infected patients, the decision to withdraw them in patients with nephropathies cannot be based simply on conjecture. Conversely, they cannot be continued in the face of kidney- and life-threatening situations, thereby putting the clinician on the horns of a true dilemma.

Prospective studies detecting mitochondrial cytopathy in HAART-treated patients with renal abnormalities by measuring pre- and postprandial lactate/pyruvate ratios, and by evaluating mtDNA heteroplasmy and functional deficit of mtDNA-encoded respiratory chain enzymes on renal biopsies should help to assess this issue.

IS RTI-RELATED TUBULAR TOXICITY SYNERGISTIC WITH HIV TUBULAR REPLICATION?

The tubule is the segment predominantly targeted by the renal toxicity of anti-HIV drugs. Consequently,

one wonders if this tubular sensitivity is worsened by HIV-1 replication in tubular cells [12]. No studies have compared the *in vitro* cytotoxicity of RTIs between HIV-infected and control tubular cells. Moreover, the comparison of the RTI-related renal tubular toxicity incidence between clinical trials evaluating RTI in HIV-infected patients and clinical trials evaluating RTI in non-HIV-infected patients (patients with hepatitis B) is not helpful since doses of cidofovir are different. Thus, there is at present no scientific argument that favors a synergistic role in the renal tubule of drug toxicity and HIV-1 replication.

The likely beneficial effect of HAART on progression of renal failure in HIVAN strongly suggests that the benefits of HAART outweigh these theoretical risks. However, we advocate particularly close monitoring for renal side-effects in this situation.

LONG-TERM RENAL TOXICITY OF ANTIRETROVIRAL TREATMENTS AND RENAL SCARRING

Chronic renal abnormalities are frequently observed in HIV-infected individuals. In this population of patients, prevention of evolution toward chronic renal failure is a crucial challenge. Two main possible pejorative roles of antiviral treatments should be considered, their long-term renal toxicity and their role in renal scarring after acute adverse events.

Usually, the diagnosis of renal toxicity of antiretroviral treatments is evoked when patients experience acute renal abnormalities. However, chronic renal abnormalities are frequent in HAART-treated patients and the renal toxicity of antiviral treatments may be underappreciated in the pathogenesis of their nephropathies. Therefore, from a theoretical point of view, the insidious long-term renal toxicity of antiretroviral treatments should be taken in account in renal failure progression and long-term longitudinal studies should be initiated to answer this question.

Moreover, in the prospective studies evaluating safety and efficacy of indinavir or other RTIs, a proportion of patients with treatment-related acute renal failure did not recover their baseline renal function (see “*adefovir*” and “*indinavir*” sections above). These data underline the possibility of permanent renal damage after acute renal injury related to antiretroviral treatment.

THREATS IN PATIENTS WITH CHRONIC KIDNEY DISEASES AND REQUIRING ANTI-HIV THERAPY

When antiretroviral treatment is required in HIV-infected patients with previous nephropathy, related or unrelated to HIV infection, two nonexclusive clinical

Table 2. Principles of the pharmacokinetic modifications according to the glomerular filtration rate (GFR) and the necessary dose adjustment for anti-human immunodeficiency virus (HIV) medication

Antiretroviral subfamily	Generic name/trade name	Dose adaptation
Protease inhibitors	Amprenavir/Agenerase	No adaptation, contraindication of oral suspension in case of GFR < 80 mL/min because of propyleneglycol in excipient
	Indinavir/Crixivan	No data
	Lopinavir (plus ritonavir)/Kaletra	No adaptation
	Nelfinavir/Viracept	No data
	Ritonavir/Norvir	No data
	Saquinavir/Invirase or Fortovase	No adaptation
Nucleoside reverse transcriptase inhibitors	Abacavir/Ziagen	No adaptation, no data for end-stage renal failure
	Didanosine/Videx	Daily dosage for an adult weighing ≥ 60 kg GFR ≥ 60 mL/min, 400 mg GFR = 30–59 mL/min, 200 mg GFR = 10–29 mL/min, 150 mg once daily GFR < 10 mL/min, 100 mg once daily, after hemodialysis
	Lamivudine/Epivir	Daily dosage for an adult GFR ≥ 50 mL/min, 300 mg GFR = 30–49 mL/min, 150 mg GFR = 15–29 mL/min, 100 mg GFR = 5–14 mL/min, 50 mg GFR < 5 mL/min, 25 mg
	Stavudine/Zerit	Daily dosage for an adult weighing ≥ 60 kg GFR > 50 mL/min, 40 mg twice daily GFR = 26–50 mL/min, 20 mg twice daily GFR < 25 mL/min, 20 mg once daily, after hemodialysis
	Zalcitabine/Hivid	GFR = 10–40 mL/min, 0.75 mg twice daily GFR < 10 mL/min, 0.75 mg once daily
	Zidovudine (azidothymidine)/Retrovir	GFR ≥ 10 mL/min, 500 to 600 mg a day GFR < 10 mL/min, 300 to 400 mg a day
	Tenofovir disoproxil fumarate/Viread	GFR ≥ 50 mL/min, 245 mg a day GFR = 30–49 mL/min, 245 mg every 48 hours GFR = 10–29 mL/min, 245 mg every 72 or 96 hours Patient treated by hemodialysis, 245 mg once a week after hemodialysis
Nucleotide reverse transcriptase inhibitors	Efavirenz/Sustiva	No data
	Nevirapine/Viramune	GFR ≥ 20 mL/min, no adaptation GFR < 20 mL/min, no data Hemodialysis, add 200 mg after hemodialysis

Sources are the official guidelines provided by drug manufacturers.

aspects should be discussed. For each drug, one should measure the possible increased risk of systemic side-effects resulting from the accumulation of drugs or of their metabolites, and the possible risk of aggravation of renal disease, the former possibly contributing to the latter and vice versa. Murphy, O'Hearn, and Chou [79] recently published the case of a patient who illustrates these difficulties. A 49-year-old patient with chronic renal failure (GFR estimated at 41 mL/min) was admitted to the intensive care unit for an ultimately fatal severe lactic acidosis and acute renal failure few weeks after his antiretroviral treatment had been changed to didanosine (without adaptation of the dosage to his reduced GFR), tenofovir despite renal failure, amprenavir, and ritonavir. The authors comment on the increased mitochondrial toxicity of the tenofovir/didanosine association in the context of chronic renal failure leading to their accumulation and worsening the renal failure.

The pharmacokinetic modifications according to the GFR and the necessary adaptation of dose for each anti-HIV medication are not detailed here. Their principles are summarized in Table 2 and in two recent publications [84, 85].

RECOMMENDATIONS TO CLINICIANS IN CASE OF PROGRESSIVE RENAL DISEASE IN HIV-INFECTED PATIENTS RECEIVING HAART

Despite drug adjustment, some HIV-infected patients experience progressive renal disease. The main challenge for the clinician is to determine the etiology of the evolving nephropathy in order to initiate specific therapeutic intervention in addition to symptomatic measures [5].

In the setting of an HIV infection, four nonexclusive etiopathogenic groups of nephropathy should be discussed: (1) HIV-related nephropathies such

Table 3. Determining cause of renal disease in human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy (HAART) (functional and obstructive renal failure being ruled out)

Renal syndrome	Clinical and urinary abnormalities	Etiologies	Interest of renal histology
Glomerular nephropathy syndrome	Nephrotic range proteinuria, including albuminuria; +/- hematuria; +/- systemic hypertension	HIVAN; HIV-associated immune glomerulonephritis; hepatitis B virus related-glomerulonephritis; hepatitis C virus related-glomerulonephritis; other infectious glomerulonephritis; amyloidosis	Yes (except in patent context of HIVAN)
Vascular nephropathy syndrome	Systemic hypertension; low-range proteinuria; inconstant hematuria; +/- schistocytic hemolysis and thrombocytopenia (in TMA only)	HIV-associated TMA; TMA unrelated to HIV; ischemic nephropathy; renal infarction	No
Tubulointerstitial nephropathy syndrome	Low-range non glomerular proteinuria (composed of low-molecular-weight proteins such as retinol-binding protein and/or α_1 microglobulin and/or β_2 microglobulin); +/- tubular dysfunction (Fanconi's syndrome, tubular acidosis, nephrogenic diabetes insipidus); no hypertension; no hematuria	Drug nephrotoxicity; infectious tubulointerstitial nephritis, including mycobacterial infections	?

Abbreviations are: HIVAN, HIV-associated nephropathy; TMA, thrombotic microangiopathy. The list of diagnosis according to the renal syndrome is not exhaustive but only indicative of the most frequent causes in the context of HIV-infected patients receiving HAART (an extensive inventory should include diseases such as primary glomerulonephritis, not listed here because unrelated to the context).

as HIVAN, HIV-related glomerulonephritis or HIV-associated thrombotic microangiopathy (TMA); (2) renal diseases related to the immune deficiency such as those induced by viral coinfection, bacterial, or parasite infection, or lymphoproliferative diseases; (3) nephropathies related to drug toxicity, including antiretroviral therapy side-effects; and (4) nephropathies unrelated to the HIV infection its consequences and treatments.

Renal and extrarenal symptomatology is of particular interest in deciding between these possibilities. Typically, usual clinical characteristics and laboratory findings will be helpful, at least to define the general type of the nephropathy: glomerular, vascular, or tubulointerstitial. According to the renal syndrome, the clinician will attempt to distinguish between possible causes from each of the four etiopathogenic groups of nephropathies defined above. Depending on situation, renal biopsy may be indicated. Table 3 lists the most frequent causes of nephropathies in HIV-infected patients except for those from etiopathogenic group 4, unrelated to the HIV infection context.

Among the glomerular nephropathies, HIV-related lesions (HIVAN and HIV-associated glomerulonephritis) and glomerulonephritis complicating hepatitis B and/or C coinfection are the most frequently observed. Proliferative glomerulonephritis may also occur as a complication of bacterial or parasitic infections. Renal histology will be very helpful in equivocal situations and should be performed if the potential diagnosis implies significant changes in therapy.

In case of acute vascular nephropathy with severe hypertension and TMA syndrome, HIV-related TMA or TMA associated with opportunistic infection or lympho-

proliferative diseases are sought. Renal histology usually confirms the diagnosis with TMA lesions in small renal arteries and/or in glomerular capillaries, but is rarely helpful in determining the etiology. Involvement of main renal arteries may also occur in patients receiving HAART because they are at high risk for premature atherosclerosis [86, 87]. Progressive ischemic nephropathy responsible for chronic or subacute renal failure with vascular nephropathy syndrome and renal infarction are the most frequent complications of renal atherosclerosis in HAART-treated patients [10] (personal observations).

In patients with acute tubulointerstitial syndrome, usual causes of acute tubular necrosis are easily recognized. However, in HIV patients, tubulointerstitial nephropathies are usually more insidious, with tubular dysfunction such as Fanconi's syndrome, nephrogenic diabetes insipidus, or tubular acidosis, usually preceding the increase in creatinine level. Particularly in this situation, two diagnoses should be considered, infectious tubulointerstitial nephritis due to mycobacteria or other organisms or, more frequently, drug nephrotoxicity since the tubules are predominantly targeted by toxicity of anti-HIV drugs (see above and Table 1). Extrarenal clinical manifestations and renal histology may facilitate the diagnosis of infectious interstitial nephritis. Regarding drug toxicity, an attentive chronologic analysis comparing the evolution of the renal disease and the introduction of potentially nephrotoxic treatments may be helpful in incriminating a particular drug. However, in most cases, a specific drug cannot be definitely blamed for the kidney disease. Renal histology is usually of little help since tubular and interstitial lesions are nonspecific and its main interest is to eliminate other causes of renal diseases.

Occasionally, the effect of withdrawal of candidate drugs on regression or stabilization of renal disease will be informative. In more severe cases with life-threatening or severe renal-threatening situations potentially related to drug toxicity, withdrawal of all antiretroviral treatment may be necessary. If a precise drug can be identified, withdrawal and subsequent modification of the antiviral regimen is indicated, while attempting to maintain adequate viral suppression special attention should be paid to the prevention of HIV resistance which may result from therapeutic modifications.

Therefore, given the large range of kidney diseases that may occur in HIV patients on HAART, each case should be analyzed and discussed independently regarding benefits and risks of drug withdrawal.

CONCLUSION

HAART has dramatically improved survival in HIV-infected patients. However, precautions should be taken to prevent HAART-related nephrotoxicity or systemic life-threatening side-effects whose risk may be increased by renal failure. Many questions remain about the pathophysiology of drug toxicity, but some simple rules can already be applied to avoid having these patients experience new health complications.

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