Antiretroviral Nephrotoxicities

Mohamed G. Atta, MD, MPH,* Gilbert Deray, MD,† and Gregory M. Lucas, MD, PhD‡

Summary: With the introduction of combination antiretroviral therapy, there have been substantial declines in both morbidity and mortality associated with human immunodeficiency virus (HIV)-1 infection. However, data increasingly indicate that HIV-1–infected individuals are faced with accelerated rates of chronic diseases that afflict the general population such as diabetes mellitus, hypertension, and dyslipidemia, as well as cardiovascular, liver, and kidney diseases. Furthermore, this population is exposed to a variety of adverse effects from long-term use of antiretroviral medications, which may cause clinically important renal toxicities. However, it often is challenging to distinguish antiretroviral-related renal toxicity from either direct effects of HIV-1 on the kidney or from a multitude of non–HIV-related kidney diseases. A timely and coordinated effort by the HIV primary provider and a nephrologist is likely to facilitate the evaluation of HIV-1–infected patients with new kidney problems.

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The introduction of combination antiretroviral therapy (ART) in the mid-1990s has greatly changed the face of human immunodeficiency virus (HIV)-1 infection not only by improving survival rates but also by reducing the morbidity associated with the infection.1-4 Recent decline and attenuation of HIV-associated nephropathy, the most aggressive form of kidney disease in HIV-infected individuals, has been linked to the use of these agents.5-7 There are 5 main classes of ART drugs that target different stages of the HIV-1 cycle. The first class is entry inhibitors: these agents interfere with viral entry into the cell by binding to viral envelope proteins and preventing attachment and entry into CD4+ cells. At present, Food and Drug Administration (FDA)-approved agents are available that target 2 distinct steps in viral entry, cellular chemokine receptor 5 (CCR5) binding and membrane fusion. Second, nucleoside reverse transcriptase inhibitors (NRTIs): these agents inhibit viral replication by chain termination. They are incorporated into growing DNA strands by HIV-1 reverse transcriptase at much higher rates than by host cellular polymerases. Third, nonnucleoside reverse transcriptase inhibitors (NNRTIs): similar to NRTIs, these agents also block viral replication by interfering with reverse transcriptase. However, NNRTIs bind reverse transcriptase at a different site from NRTIs and therefore have no cross-resistance with the NRTI class. Fourth, protease inhibitors (PIs): these drugs inhibit the protease enzyme, which plays a key role in the assembly of the new virus particles. Fifth, integrase inhibitors: raltegravir potassium (Isentress; Merck, Whitehouse Station, NJ) is the first member of a new class of ART, integrase inhibitors. This new agent is used in multidrug-resistant HIV-1 infection, and prevents viral replication by inhibiting viral DNA insertion into the host cellular genome.

Antiretroviral regimens typically include 3 drugs, from at least 2 different drug classes. The high replication rate of HIV-1 and its error-prone reverse transcriptase lead to the rapid emergence of drug-resistance mutations when single-drug therapy is used, a situation that is greatly ameliorated by multidrug therapy.
Table 1 summarizes the characteristics of different antiretroviral agents and standard adult dose in individuals with and without kidney disease. Of the available ART classes, NRTIs generally require dose adjustment in patients with kidney disease, the one exception being abacavir sulfate (Ziagen; GlaxoSmithKline, Middlesex, United Kingdom), which is metabolized primarily by the liver. Pharmacokinetics of ART have been detailed elsewhere.

A variety of adverse effects of ART have been recognized, including metabolic, lipid, and bone toxicities. Importantly, renal toxicity has been associated with several of these agents (Table 2).

<table>
<thead>
<tr>
<th>Name</th>
<th>Form</th>
<th>Standard Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs Inhibit gene copying process</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC, Ziagen)</td>
<td>300-mg tab</td>
<td>600 mg/d</td>
</tr>
<tr>
<td>Atripla</td>
<td>TDF 300 mg + FTC 200 mg + EVF 600 mg (NNRTI)</td>
<td>1 tab/d</td>
</tr>
<tr>
<td>Combivir (CBV)</td>
<td>AZT 300 mg + 3TC 150 mg</td>
<td>1 bid</td>
</tr>
<tr>
<td>Diadanosine (Videx; Videx EC; ddI)</td>
<td>Powder: 100, 167, 250 mg</td>
<td>&gt;60 kg: 60 kg, &lt;60 kg: Powder 250 mg bid 167 mg bid</td>
</tr>
<tr>
<td></td>
<td>EC caps: 125, 200, 250, and 400 mg bid</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine (Emtriva, FTC)</td>
<td>200-mg cap</td>
<td>200 mg qd (cap)</td>
</tr>
<tr>
<td></td>
<td>10-mg/mL solution</td>
<td>24 mL (240 mg) qd (liquid)</td>
</tr>
<tr>
<td>Epivir</td>
<td>ABC 600 mg + 3TC 300 mg</td>
<td>1 tab qd</td>
</tr>
<tr>
<td>Lamivudine (Epivir; 3TC)</td>
<td>100-, 150-, 300-mg tab 5-mg/mL solution</td>
<td>300 mg/d</td>
</tr>
<tr>
<td>Stavudine (Zerit; d4T)</td>
<td>15-, 20-, 30-, 40-mg cap 1-mg/mL solution</td>
<td>&gt;60 kg: 40 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;60 kg: 30 mg bid</td>
</tr>
<tr>
<td>Tenofovir (Viread, TDF)</td>
<td>300-mg tab</td>
<td>300 mg bid</td>
</tr>
<tr>
<td>Trizivir</td>
<td>AZT 300 mg + 3TC 150 mg + ABC 300 mg</td>
<td>1 tab bid</td>
</tr>
<tr>
<td>Truvada</td>
<td>TDF 300 mg + FTC 200 mg</td>
<td>1 tab qd</td>
</tr>
<tr>
<td>Zidovudine (Retrovir, GlaxoSmithKline)</td>
<td>100-, 300-mg tab</td>
<td>300 mg bid</td>
</tr>
<tr>
<td><strong>NNRTIs Inhibit gene coping enzyme</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine (Rescriptor, DLV)</td>
<td>100-, 200-mg tabs</td>
<td>400 mg tid</td>
</tr>
<tr>
<td>Efavirenz (Sustiva, EFV)</td>
<td>50-, 100-, 200-mg caps, 600-mg tabs</td>
<td>600 mg hs</td>
</tr>
<tr>
<td>Nevirapine (Viramune, NVP)</td>
<td>200-mg tab 50-mg/5-mL suspension</td>
<td>200 mg qd × 14 d, then 200 mg bid</td>
</tr>
<tr>
<td>Etravirine or TMC125 (Intelicence)</td>
<td>100-mg tabs</td>
<td>200 mg bid</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (Reyataz, ATV)</td>
<td>100-, 150-, 200-, and 300-mg caps</td>
<td>400 mg qd, ATV 300/RTV 100 qd</td>
</tr>
<tr>
<td>Darunavir (Prezista, DRV)</td>
<td>300-mg tabs</td>
<td>600 DRV + 100 RTV bid</td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva, FPV)</td>
<td>700-mg tabs</td>
<td>1400 mg bid or FPV 700/RTV 100 bid</td>
</tr>
<tr>
<td>Indinavir (Crixivan, IDV)</td>
<td>100-, 200-, 333-, 400-mg caps</td>
<td>800 mg every 8 h, IDV 800/RTV 100 bid</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (Kaletra, LPV/r)</td>
<td>LPV 200-mg + RTV 50-mg tab; LPV 80-mg + RTV 20-mg/mL solution</td>
<td>LPV/r 400/100 mg bid or 800/200 mg qd</td>
</tr>
<tr>
<td>Nelfinavir (Viracept, NFV)</td>
<td>250-, 625-mg tabs</td>
<td>1250 mg bid or 750 mg tid</td>
</tr>
<tr>
<td>Ritonavir (Norvir, RTV)</td>
<td>100-mg tabs</td>
<td>600 mg bid (rarely used); often used at doses of 100-400 mg/d to boost concentrations of other PIs</td>
</tr>
<tr>
<td>Saquinavir (Invirase, SQV)</td>
<td>200-mg cap, 500-mg tab</td>
<td>SQV 1000/RTV 100 mg bid</td>
</tr>
<tr>
<td>Tipranavir (Aptivus, TPV)</td>
<td>250-mg cap</td>
<td>TPV 500/RTV 100 mg bid</td>
</tr>
<tr>
<td><strong>Entry inhibitor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (T20)</td>
<td>90-mg single-dose vial</td>
<td>90 mg subcutaneously bid</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>150-, 300-mg tabs</td>
<td>150, 300, or 600 mg bid depending on co-administered drugs</td>
</tr>
<tr>
<td><strong>Integrase inhibitor Inhibit integrase</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (Protease intervening)</td>
<td>400-mg tabs</td>
<td>400 mg bid</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; CrCl, creatinine clearance; tab, tablet.
Most of the renal toxicities are type B adverse drug reactions. In contrast to the more common type A adverse drug reactions, type B adverse reactions are generally idiosyncratic, not dose dependent, and have less pharmacologic predictability because they are mostly driven by uncharacterized host factors. Consequently, these toxicities represent a significant risk to both quality of life and compliance with therapy among HIV-infected individuals. Established renal adverse reactions have been associated with the use of several NRTIs and PIs. Because renal transporter-mediated mechanisms are involved in the elimination of these
agents, intracellular accumulation and potential toxicities may occur if these mechanisms are perturbed. Organic anion transporters (OATs) and organic cation transporters are expressed on the basolateral membrane of proximal tubular cells and mediate the uptake of NRTIs and PIs.\textsuperscript{12-18} Multidrug-resistant proteins and P-glycoproteins are expressed on the apical membrane of proximal tubular cells and mediate the efflux of these agents.\textsuperscript{13,19-25} Disruption in basolateral uptake, apical efflux, or both may result in the accumulation of these agents in the proximal tubular cells with potential toxicity. Conversely, renal transporter–mediated mechanisms are not involved in the elimination of NNRTIs, entry inhibitors, or integrase inhibitors, which may explain the less nephrotoxic profiles of these agents. Adverse renal reactions with these agents have been limited to case reports and adverse reactions reported during clinical trials. Therefore, a causative relationship has not been established with the use of these agents.

**NRTI-RELATED NEPHROTOXICITIES**

NRTIs are processed and eliminated by the kidney. The OATs have been postulated to constitute the initial step in the uptake of several NRTIs.\textsuperscript{26,27} For example, in vitro data suggests that OAT3 is the major transporter interacting with didanosine (Videx; Bristol-Myers Squibb, New York, New York) and is potentially the mediator of drug cytotoxicity.\textsuperscript{28} Similarly, OAT1 serves as the primary substrate for transporting acyclic nucleoside phosphonates such as adefovir dipivoxil (Hepsera; Gilead Sciences, Foster City, CA), cidofovir (Vistide, Gilead Sciences), and tenofovir disoproxil fumarate (Viread, Gilead Sciences).\textsuperscript{29,31}

Hyperlactatemia is a relatively frequent adverse event associated with the use of NRTIs. It can be detected in up to 20% to 30% of patients treated with NRTIs, typically after several months of therapy. In cross-sectional and longitudinal studies in which lactate was measured in ambulatory HIV-infected patients, most lactate increases were small in magnitude (lactate acid, $\leq 2.5$ mmol/L), often transient, and not associated with identifiable symptoms.\textsuperscript{32-34} Severe hyperlactatemia (lactate acid, $>5-10$ mmol/L) can occur in up to 1.5% to 2.5% of patients and is associated with a mortality rate of more than 50%.\textsuperscript{35,36} Stavudine (Zerit; Bristol-Myers Squibb) and didanosine are clearly the most commonly implicated NRTIs, although all agents in this class have been linked with hyperlactatemia.\textsuperscript{34,57,38} Clinical manifestations range from mild nausea, abdominal discomfort, or weight loss, to severe intractable lactic acidosis, leading to coma and multi-organ failure.\textsuperscript{36}

Among NRTIs currently approved for the treatment of HIV-1, renal toxicity has been most clearly established with tenofovir. Renal toxicity also is well-described with 2 NRTIs that are related structurally to tenofovir: cidofovir, which is FDA-approved for the treatment of cytomegalovirus retinitis in HIV-1–infected individuals,\textsuperscript{39} and adefovir, which originally was developed for the treatment of HIV-1 and is now FDA-approved for the treatment of hepatitis B virus infection. Nephrotoxicity occurred in up to 30% of patients treated with the dose of adefovir used in HIV-1 treatment (120 mg/d). In 1999, an expert panel recommended against FDA approval of adefovir for HIV-1 treatment because of concerns about renal toxicity. The manufacturer discontinued adefovir development for HIV-1 treatment, but continued its development for the treatment of chronic hepatitis B virus infection. Interestingly, the lower dose of adefovir used to treat hepatitis B (10 mg/d) generally is not associated with nephrotoxicity. Tenofovir-associated nephrotoxicity is much less frequent than that observed with cidofovir or high-dose adefovir.

**Tenofovir Toxicity**

A favorable pharmacokinetic profile, good antiviral potency, tolerability, and a lower incidence of mitochondrial toxicities seen with other NRTI (eg, lactic acidosis, lipodystrophy, and neuropathy) have made tenofovir the most commonly prescribed NRTI in the United States and western and central Europe. Almost two thirds of all treated HIV-1–infected patients currently are receiving tenofovir. Fig. 1 displays the number of individuals infected with HIV-1 in the United States and the most commonly prescribed NRTIs. Similar trends are seen in western and central Europe regarding NRTI use. Tenofovir is used most often with emtricitabine (Emtriva; Gilead Sciences) as a combination preparation (Truvada), or with lamivudine.
(Epivir; GlaxoSmithKline) in combination with either an NNRTI or a PI. It also can be used with emtricitabine and efavirenz (Sustiva; Bristol-Myers Squibb) in a fixed dose combination tablet (Atripla). The drug has been associated with renal tubular toxicity resulting in acute tubular injury, Fanconi syndrome, nephrogenic diabetes insipidus, and acute or chronic reduction in glomerular filtration rate.

The mechanism underlying these renal toxicities has not been elucidated fully. Adefovir, cidofovir, and tenofovir are excreted unchanged in the urine, with renal clearances of 205, 130, and 150 mL/h/kg, respectively, consistent with significant active tubular secretion.39-42 Because intracellular drug accumulation is a function of uptake and secretion, enhanced uptake via OAT1 on the basolateral membrane or impaired

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### Table 2. Renal Adverse Effects of ART

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nephrotoxic Effects</th>
<th>Frequency</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Acute interstitial nephritis and Fanconi syndrome (1 case report each)</td>
<td>Rare</td>
<td>94,95</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Acute renal failure, Fanconi syndrome, nephrogenic diabetes insipidus, lactic acidosis</td>
<td>1.5%-2.5%</td>
<td>46,96,97</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Renal tubular acidosis and hypophosphatemia (case report)</td>
<td>Rare</td>
<td>98</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Acute renal failure, Fanconi syndrome/proximal tubule dysfunction, nephrogenic diabetes insipidus</td>
<td>0.5%-7%</td>
<td>43,44,49,55-58, 60-62,99,100</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Acute renal failure</td>
<td>Rare</td>
<td>64</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nephrolithiasis</td>
<td>Rare</td>
<td>66,101</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Acute renal failure</td>
<td>Rare</td>
<td>65</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Acute renal failure</td>
<td>Rare</td>
<td>68</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>No nephrotoxic effects reported with amprnavir, fosamprenavir, lopinavir, darunavir, or tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Nephrolithiasis</td>
<td>1%</td>
<td>87-90</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Intratubular crystallization, nephrolithiasis, acute interstitial nephritis, chronic kidney disease, papillary necrosis</td>
<td>8%-19%</td>
<td>84-86,102-111</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td>No nephrotoxic effects reported with amprnavir, fosamprenavir, lopinavir, darunavir, or tipranavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Nephrolithiasis (case report)</td>
<td>Rare</td>
<td>70</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Acute renal failure, acute tubular necrosis</td>
<td>Rare</td>
<td>71-75</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Nephrolithiasis</td>
<td>Rare</td>
<td>69</td>
</tr>
<tr>
<td><strong>Entry inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfvirtide</td>
<td>Membranoproliferative glomerulonephritis (1 case)</td>
<td>Rare</td>
<td>91</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>None reported (recently approved for use by FDA)</td>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Vicriviroc</td>
<td>Still under investigation</td>
<td>Unknown</td>
<td>92</td>
</tr>
<tr>
<td><strong>Integrase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Acute renal failure</td>
<td>Rare</td>
<td>93</td>
</tr>
</tbody>
</table>
efflux via one or more of the multidrug-resistant proteins will, in theory, result in drug accumulation and potential toxicity. Mitochondrial DNA depletion owing to inhibition of DNA polymerase γ, the major enzyme responsible for replication of mitochondrial DNA, has been proposed as a mechanism of systemic and renal toxicity of NRTIs. Although this mechanism may explain the development of Fanconi syndrome in association with the use of didanosine, it is important to note that tenofovir is a weaker inhibitor of DNA polymerase γ than other NRTIs.

Although clinical and postmarketing trials involving tenofovir failed to show any serious renal toxicities, evidence from case reports and cohort studies have shown an association between the use of tenofovir and nephrotoxicity. In the open-label, noninferiority study involving 517 HIV-1–infected naive patients who were assigned randomly to receive either tenofovir, emtricitabine, and efavirenz once daily or a regimen of fixed-dose zidovudine and lamivudine twice daily plus efavirenz once daily, no tenofovir-related serious adverse renal events were reported. Conversely, a retrospective analysis of a large observational cohort of patients who received either tenofovir (n = 344) or an alternative NRTI (n = 314) showed that the use of tenofovir was associated with a greater decline in renal function compared with the use of other NRTIs, although the clinical significance was unclear. This discrepancy may be partially explained by the inherent differences between clinical trials and observational studies of real-world practice. For example, patients in clinical trials are more likely to have normal renal function and fewer comorbid conditions than subjects followed up in cohort studies. The low absolute rate of proximal tubulopathy also may account for the inability to detect renal toxicity in clinical trials. Further, PIs, which have been suggested to increase the risk of tenofovir nephrotoxicity, were not used in clinical trials.

Clinically, the spectrum of tenofovir-associated nephrotoxicity spans mild renal tubular dysfunction with subclinical decline of renal function to the classic Fanconi syndrome. Although the clinical findings of Fanconi syndrome have been well described, standardized criteria for the diagnosis of tenofovir-induced Fanconi syndrome have not been established. Clinical features include glycosuria in the setting of normal serum glucose, phosphate wasting with hypophosphatemia (phosphate diabetes), subnephrotic range proteinuria (rarely in the nephrotic range), acidosis, hypokalemia, and acute renal failure. Some patients have been reported to present with evidence of nephrogenic diabetes insipidus. Risk factors for the development of tenofovir-induced nephrotoxicity include underlying renal dysfunction, low CD4 count, and low body weight. The use of protease inhibitors, particularly ritonavir (Norvir; Abbott, Abbott Park, IL), has been suggested, although not proven, to play a role in the nephrotoxicity of tenofovir. In the 164 subjects reported to the FDA with tenofovir-induced Fanconi syndrome, 74% were on ritonavir, and 83% were on pro-
**Antiretroviral nephrotoxicities**

NNRTI NEPHROTOXICITIES

No renal transport mechanism has been identified in the excretion of NNRTIs. Therefore, this class has been considered to be of lesser nephrotoxic potential, and clinical evidence of NNRTI-mediated renal toxicity is scant. Rhabdomyolysis with acute renal failure was described in a single case owing to potential interaction of delavirdine mesylate (Rescriptor; Pfizer, New York, NY) with atorvastatin (Lipitor; Pfizer).\(^{64}\) Nevirapine (Viramune; Boehringer Ingelheim, Ingelheim, Germany) has been implicated in the development of acute renal failure with rash and eosinophilia in a pregnant patient.\(^{65}\) Efavirenz has been recently linked to nephrolithiasis in 2 patients.\(^{66,67}\) Acute renal failure has been reported to occur in 1% of patients assigned to etravirine (Intelect; Tibotec, Bridgewater, NJ) in clinical trials.\(^{68}\)

PROTEASE INHIBITOR NEPHROTOXICITIES

The use of indinavir sulfate (Crixivan; Merck) and atazanavir sulfate (Reyataz; Bristol-Myers Squibb) has been linked to nephrolithiasis, the former to a much greater degree. Renal calculi also have been reported to develop de novo in a patient taking saquinavir mesylate (Invirase; Roche Laboratories, Nutley, NJ)\(^{69}\) and in a patient taking nelfinavir mesylate (Viracept; Agouron Pharmaceuticals, La Jolla, CA).\(^{70}\) Although a causal relationship has not been well established, ritonavir has been implicated as a cause of acute renal failure in several reports.\(^{71-75}\) No nephrotoxic effects have been reported with amprenavir (Agenerase; GlaxoSmithKline), fosamprenavir calcium (Lexiva; GlaxoSmithKline), lopinavir (Kaletra; Abbott), darunavir (Prezista; Tibotec), or tipranavir (Aptivus; Boehringer Ingelheim).

**Indinavir**

As the best tolerated and most effective of the early PIs to be released in the mid-1990s, indinavir was one of the most widely prescribed drugs for the treatment of HIV-1 infection for several years. Indinavir is the prototype for ART-induced crystal nephropathy and nephrolithiasis. In addition, the drug also has been associated with severe acute and chronic interstitial nephritis. Although 80% of the administered dose is metabolized in the liver, the remainder is eliminated by the kidneys, largely excreted as the parent molecule.\(^{76}\) The drug’s solubility in water is pH-dependent, greater than 100 mg/mL at a pH of less than 3.5, and extremely low at physiologic pH (0.03 mg/L at pH 6).\(^{77}\) Consequently, asymptomatic indinavir crystalluria is common with indinavir use occurring in two thirds of treated patients,\(^{78,79}\) whereas the incidence of symptomatic crystalluria or nephrolithiasis has been estimated at 8% to 19% of patients on chronic therapy.\(^{80-82}\)

On urinary examination (Fig. 2), indinavir crystals appear as plate-like rectangles, fan-shaped, or starburst forms.\(^{83}\) The crystals also can be identified on renal biopsy (Fig. 2). Other common urinary abnormalities include pyuria and microscopic hematuria.\(^{84,86}\) Clinically, patients present with the typical syndrome of renal colic manifested as flank pain, dysuria, urgency, and urinary frequency with or without gross hematuria. Low lean body mass was shown to be the strongest risk for the development of urologic symptoms in patients receiving indinavir.\(^{80}\) Other risk factors include higher indinavir doses, use of ritonavir as a pharmacologic boosting agent, warm climates, and suboptimal daily fluid intake. In developed countries, indinavir has largely been replaced by next-generation PIs and rarely is used.

**Atazanavir**

Atazanavir use initially was implicated as a potential cause of nephrolithiasis in case reports.\(^{87,88}\) Subsequently, 30 reported cases of atazanavir-associated nephrolithiasis over a 4-year period were discovered on review of the Adverse Event Reporting System database of the FDA.\(^{89}\) A more recent study estimated a
prevalence of atazanavir stones to be 0.97% among those taking the drug. A Although no associated risk factors have been found, atazanavir stones appear to form in alkaline urine. On urinary examination (Fig. 2), atazanavir crystals appear as rod-like forms. Although relatively uncommon in those taking the drug, atazanavir nephrolithiasis should be considered in patients who develop renal colic; and may be confirmed by biochemical stone analysis. In contrast to indinavir, atazanavir has not been associated with acute or chronic interstitial renal disease.

ENTRY INHIBITORS

HIV-1 Fusion Inhibitor

Enfuvirtide (Fuzeon; Roche Laboratories) is a 36-amino acid peptide that binds to envelope glycoprotein 41 of HIV-1 and inhibits the fusion of the virus and the membrane of the CD4-positive cells. Because of its chemical structure, enfuvirtide must be administered by subcutaneous injection twice daily. 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 a previous history of proteinuria and hematuria showed a hypersensitivity reaction with a membranoproliferative nephritis. B However, renal toxicity is not a substantial consideration with the use of this drug.

CCR5 Antagonists

CCR5 antagonists represent a new class of agents aimed at inhibiting viral entry. After binding of glycoprotein 120 to the CD4 receptor, CCR5 antagonists inhibit the interaction of glycoprotein 120 to the co-receptor, an integral step in the fusion of HIV to the host cell. This may have an impact on the treatment of patients with multidrug-resistant HIV-1. No renal toxicity has been reported with the use of Ma-
raviroc (Selzentry; Pfizer). The other CCR5 inhibitor, Vicriviroc (Schering-Plough, Kenilworth, NJ) is still an investigational agent undergoing clinical trials.92

**INTEGRASE INHIBITORS**

Although human beings lack the integrase enzyme and therefore toxicities caused by integrase inhibition are not expected, renal failure was among serious drug-related adverse events reported in randomized, double-blind, placebo-controlled trials in treatment-experienced HIV-1-infected patients receiving raltegravir 600 mg daily,93 and also with 400 mg twice daily in combination with optimized background therapy (Isentress, Merck). This may, in part, be owing to the high incidence of vomiting and diarrhea associated with the drug.

**CONCLUSIONS**

ART-induced renal toxicity is a relatively common event in patients infected with HIV-1. Several of these medications have been shown to elicit a variety of renal diseases and therefore drug toxicity should always be considered in this population. With earlier identification, withdrawal of the culprit drug may result in full recovery or stabilization of the renal function. This requires attentive care and close monitoring of patients on these medications.

**REFERENCES**


