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HIV medication-based urolithiasis

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Abstract

Drug-induced renal calculi represent 1–2% of all renal calculi. In the last decade, drugs used for the treatment of HIV-infected patients have become the most frequent cause of drug-containing urinary calculi. Among these agents, protease inhibitors (PIs) are well known to induce kidney stones, especially indinavir and atazanavir, and more recently darunavir. Urolithiasis attributable to other PIs has also been reported in clinical cases such as those during non-PI use. Antiretroviral drug-induced calculi deserve consideration because most of them are potentially preventable. This article summarizes the diagnosis, epidemiology, prevention and management of antiretroviral drug-induced urolithiasis.

Keywords: antiretroviral; HIV; renal failure; urolithiasis

Introduction

In North America, the lifetime risk of urolithiasis is estimated to be 10–15%, with a 50% rate of recurrence over 10 years [1]. The cost of the acute management of urolithiasis in the USA is estimated to be $1.83 billion annually [2]. A recent analysis of >3 million people in the general population in Alberta, Canada [3] found that development of even a single kidney stone was associated with a significant increase in the likelihood of adverse kidney outcomes including end-stage renal disease, which can necessitate dialysis or transplantation.

Stones caused by medications represent ∼1–2% of all uroliths [4]. The term 'medication-based urolithiasis' refers to stones formed by direct crystallization of a poorly soluble, renally excreted medication or its metabolites, as well as to stones formed when medications crystallize around previously formed urinary stones. As new and more effective combination antiretroviral therapy for the treatment of HIV infection has become available, patients have developed iatrogenic complications involving various organs including kidneys and urolithiasis (Table 1). Nephrolithiasis associated with antiretrovirals can cause significant morbidity, including renal dysfunction and hydronephrosis. Lithotripsy, ureteral stent insertion, nephrostomy tube placement or endoscopic stone removal was needed in a subset of cases. Some cases of nephrolithiasis resulted in the discontinuation of drugs. It is thus important to elucidate the incidence and management of antiretroviral-associated renal stones, since renal stones are risk factors for chronic kidney diseases (CKDs), an important comorbidity associated with HIV infection and death [5–7]. In this article, the diagnosis, epidemiology, prevention and management of antiretroviral drugs-induced urolithiasis are reviewed.

Protease inhibitor-based urolithiasis

Kidney stones are more common in HIV patients taking protease inhibitors (PIs). This was mainly the case with indinavir in the 1990s, and this is still the case today with atazanavir. Other PIs such as nelfinavir, amprenavir, saquinavir, ritonavir and darunavir have also been reported to cause urolithiasis or to crystallize in urine. It is therefore important to obtain and analyse the stones.

Indinavir

Among antiretroviral agents, indinavir is well known to induce kidney stones. Indinavir has been associated with asymptomatic crystalluria, nephrolithiasis and elevated serum creatinine levels [8–20] (Table 2). Only 9.2% of patients had to discontinue therapy [12].

In the clinical setting, many factors may increase the risk of indinavir crystallization in urine (Table 3) [10, 13, 21–23]. Indinavir is primarily metabolized by the liver with 20% eliminated through urine, approximately half of which is unchanged [24]. Indinavir crystallization occurs at a urine concentration of 100 mg/L, which corresponds to a plasma concentration of 6.4 mg/L [25]. The peak plasma concentration of indinavir in patients at the recommended dose of boosted 400–800 mg is already 8–10 mg/L [21]. Within 3 h after a typical indinavir dosage of 800 mg orally in a patient averaging 1.5 L urine output daily, the urine concentration already exceeds the limits of solubility at 200–300 mg/L, making crystal formation likely to be common [21]. Crystals of varying shapes have been described and are more common in the urine with pH ≥6 [9, 10, 26]. Urinary stones are composed primarily of indinavir monohydrate; calcium

Table 1. Antiretroviral nephrotoxicity

	Urolithiasis and/or ITP	PRTD	NDI	AKI	CKD
PIs					
Indinavir	■		■	■Obstructive	■
Atazanavir	■			■AIN	■
Ritonavir/saquinavir	■			■Pancreatorenal syndrome	
Nelfinavir	■				
Amprenavir	■				
Lopinavir	■				
Darunavir	■				
Nucleos(t)ide reverse transcriptase inhibitors					
Didanosine		■	■		
Abacavir				■AIN	
Tenofovir		■	■	■ATN	■
FTC 3TC					
Non-nucleoside reverse transcriptase inhibitors					
Efavirenz	■			■AIN	
Nevirapine				■AIN	
Etravirine					
Rilpivirine					
Anti-integrase					
Raltegravir	■				
Fusion inhibitors					
Enfivurtide				■MPGN	
CCR5 inhibitors					
MVC					

ITP, intratubular precipitation; PRTD, proximal renal tubular dysfunction; NDI, nephrogenic diabetes insipidus; AIN, acute interstitial nephritis; AKI, acute kidney injury, CKD, chronic kidney disease; MPGN, membranoproliferative glomerulonephritis.

Table 2. Prevalence of indinavir nephrotoxicity

Symptoms	Incidence (%)	Reference
Asymptomatic crystalluria	66	[12]
Symptomatic crystalluria and/or Nephrolithiasis	4–33 in chronic therapy	[12]
ARF due to interstitial nephritis, crystal nephropathy and/or obstructive nephropathy	20	[13–15]
Urothelial inflammation	74	[15]
CRF due to CIN, tubular atrophy, hypertension, NDI	Cases	[15–19]

ARF, acute renal failure; CRF, chronic renal failure; CIN, chronic interstitial nephritis; NDI, nephrogenic diabetes insipidus.

Table 3. Risk factors of indinavir crystallization [10, 13, 21–23]

Volume depletion
Individual indinavir pharmacokinetics
Hepatic insufficiency
Renal insufficiency
Plasma protein binding
Low urinary pH
Low lean body mass
HCV/HBV co-infection
Acyclovir or trimethoprim-sulfamethoxazole use

oxalate and phosphate as well as indinavir metabolites may also be present [9, 24].

Management of indinavir-associated nephrolithiasis should be conservative and includes hydration, pain control, monitoring of renal function and temporary discontinuation of the drug [12]. Furthermore, most stones are radiolucent and are not detectable with plain radiographs. It is recommended that patients who start on indinavir be monitored periodically during the first 6 months of therapy, then biannually thereafter for changes in renal function and pyuria [7]. According to current recommendations, patients receiving indinavir should be instructed to drink at least 1.5 L of liquid per day [12, 25]. Daudon *et al.* [24] recommend increasing urine output to ≥150 mL/h during the 3 h after each dose. Urinary acidification, although theoretically of benefit, is not generally recommended.

In patients who develop indinavir-related nephrolithiasis, therapy usually can be resumed after resolution of the acute episode once adequate volume status is achieved. However, not all indinavir stones resolve with conservative treatment. In some cases, surgical intervention is required. Five per cent of symptomatic indinavir stone required removal by means of ureteroscopy as given in Daudon reports [24]. Kopp *et al.* [9] observed 240 indinavir patients, of whom 7 patients (3%) had nephrolithiasis, but only 1 of whom required surgical intervention [9]. Bruce *et al.* [27] reported three patients who were receiving indinavir and who required surgical intervention for persistent symptoms. The investigators recommended upper urinary tract imaging for indinavir patients who present symptoms of urolithiasis, and prompt urological intervention when conservative therapy fails [27]. Gentle *et al.* [28] described the radiolucent gelatinous character of indinavir stones, suggesting that lithotripsy is a poor treatment choice, and recommended ureteral stenting and ureteroscopic removal of calculi for cases of symptomatic obstruction. Grunke *et al*. [29] reported an indinavir patient with nephrolithiasis and mild renal impairment; stent placement was required because the stone could not be removed by means of mechanical extraction or lithotripsy.

Atazanavir

According to current guidelines, ritonavir-boosted atazanavir (ATV/r) is one of the key first-line drugs because of its high efficacy, tolerability, favourable lipid profile and once-daily dosing [30, 31] and is widely used for both treatment-experienced and treatment-naïve HIV-infected patients. Several cases have established that atazanavir induced urolithiasis, with high concentrations of atazanavir found in the stones themselves [32, 33].

Epidemiological studies have found that exposure to atazanavir is associated with an increased incidence of renal stones compared with other PI-based regimens [34, 35].

In a retrospective study from March 2004 through February 2007 including 1134 patients treated with atazanavir, 11 of these patients (overall prevalence, 0.97%) received a diagnosis of symptomatic atazanavir-associated urolithiasis. The diagnosis of atazanavir-associated urolithiasis was determined by infrared spectrophotometry. The analysis revealed that stones contained crystals of atazanavir base without metabolites [36]. No recurrence occurred in 5 of the 6 patients who continued to receive the atazanavir therapy [36].

From December 2002 to January 2007, the US FDA's Adverse Event Reporting System identified 30 cases of nephrolithiasis in HIV-infected patients taking an atazanavir-based regimen [32]. Five patients (17%) had underlying liver disease: four patients had hepatitis C and one patient had hepatitis B. Three patients had pre-existing renal disease and five patients (17%) had a history of

nephrolithiasis. Of the 20 cases reporting complete antiretroviral information, 13 patients received concomitant therapy with tenofovir and 17 patients received 100 mg of ritonavir. Among 14 cases reporting stone analysis, 12 had atazanavir confirmed by infrared spectrophotometry or other analysis. In six cases, atazanavir concentrations in the stone ranged from 40 to 100%. In 17 cases with a complete atazanavir treatment history, the median time between atazanavir initiation and the onset of nephrolithiasis was 1.7 years (ranged from 5 weeks to 6 years). Many patients required hospitalization for management, including lithotripsy, ureteral stent insertion or endoscopic stone removal. Five patients developed renal insufficiency (four with acute renal insufficiency and one with a worsening of baseline chronic renal insufficiency) at the time of nephrolithiasis. In all the four cases of acute renal insufficiency, renal function returned to baseline after stone removal and atazanavir discontinuation. In the patient who developed a worsening of baseline chronic renal insufficiency, renal function improved but had not returned to its previous baseline after stone removal. Of the 30 cases, atazanavir was reported as discontinued in 9 cases (30%) after nephrolithiasis was diagnosed [32].

A report based only on radiological findings compared the incidence of renal stones among patients receiving ATV/r and those receiving other antiretrovirals [34]. The reported incidence of ATV/r-induced renal stones was much lower (7.3 cases per 1000 person-years), compared with 23.7 cases per 1000 person-years in Hamada's study [35]. In this last study, renal stones were diagnosed in 31 patients (23.7 cases per 1000 person-years) in the ATV/r group ($n = 465$) and in 4 patients (2.2 cases per 1000 person-years) in the other PI group ($n = 775$). ATV/r use was significantly associated with renal stones in multivariable analysis [adjusted hazard ratio, 10.44; 95% confidence interval (CI), 3.685–29.59; $P < 0.001$]. ATV/r remained a significant risk factor for renal stones in all subgroups stratified by the median values of baseline variables. In the 31 patients receiving ATV/r who developed renal stones, the median time from commencement of ATV/r to diagnosis was 24.5 months (interquartile range, 14.7–34.6 months). Of the 18 patients who continued ATV/r despite the diagnosis of renal stones, 6 (33.3%) experienced recurrence. No patient who discontinued ATV/r experienced recurrence during the observation period (250.6 person-months) [35]. Although the incidence of renal colic in patients taking atazanavir is much lower than in those taking indinavir [34, 35], de Lastours *et al.* found atazanavir crystals (Fig. 1) in the urine of 8.9% of asymptomatic patients, all taking ritonavir-boosted atazanavir. Indeed, the number of crystals found in the urine was lower (maximum 10/mm^3) than that found in indinavir-treated patients (up to 250/mm^3) [37].

Although interstitial nephropathies affect up to 13% of HIV-infected patients, ATV/r-induced interstitial nephritis remains rare including only 6 cases reported [38–41]. Brewster and Perazella [38] reported a case of acute tubulointerstitial nephritis without crystal deposit related to an atazanavir hypersensitivity reaction, occurring 4 weeks after atazanavir was started. Renal function recovered after drug discontinuation. Schmid *et al.* [40] reported three cases of acute interstitial nephritis under atazanavir/ténofovir combination, occurring between 6 and 16 weeks after starting ritonavir-boosted atazanavir. Two other cases of acute and chronic kidney injury due to intratubular atazanavir crystals with [39] or without [41] atazanavir plasma concentration overdosage who responded to steroid therapy have also been reported.

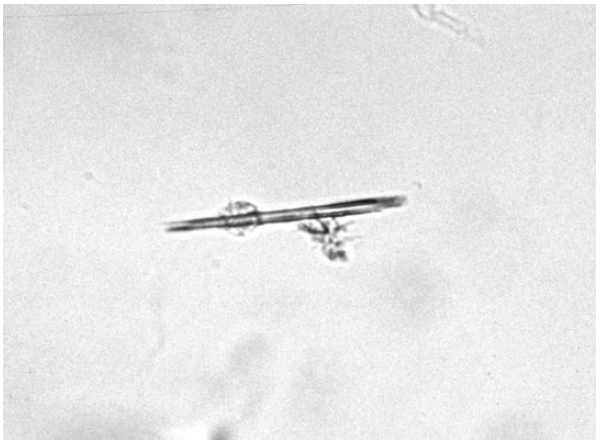

Fig. 1. Atazanavir crystal: rodlike-shaped mildly birefringent urine crystal, measuring 8–20 nm and thrusting the white cell.

The mechanism of formation of atazanavir stones is unknown. Several risk factors have been suggested: preexisting hepatic or renal impairment, past history of renal stones, high serum bilirubinaemia suggesting a slower metabolization of atazanavir; alkaline urine; chronic active hepatitis C, which may impair the liver's clearance of atazanavir and therefore increase renal elimination and longer atazanavir exposure [32, 34–36]. Data suggest that plasma concentrations of boosted atazanavir are not elevated in HIV-HCV-coinfected patients and do not correlate with liver stiffness [42].

It is, however, probably linked to urinary precipitation of pure atazanavir, as has been described for indinavir stones [24]. Atazanavir is mainly metabolized and eliminated by the liver. However, in healthy subjects, up to 7% of the drug is excreted unchanged in the urine following a single 400-mg dose [43]. Like indinavir, atazanavir is slightly soluble in water (4–5 mg/mL) and has a pH-dependent solubility (with a maximal solubility at pH 1.9).

The duration of exposure to atazanavir seems to be an important risk factor for urolithiasis, as most patients suffering from renal stones had been taking atazanavir for several years [32, 33, 36], stones occurring at an average of 2 years after the start of atazanavir treatment [35, 36].

Based on the pharmacokinetics of atazanavir, maintenance of a high urinary output and urine acidification may be helpful in preventing atazanavir crystallization and urolithiasis recurrence. Urine acidification may, however, be poorly tolerated and possibly harmful, especially for patients receiving concomitant treatment with sulphonamide derivatives. One team has suggested that a discontinuation of tenofovir could induce urolithiasis in atazanavir-treated patients because tenofovir decreases the concentration of atazanavir [44]. However, concomitant tenofovir disoproxil fumarate did not seem to be a protective factor against ATV/r-renal stones.

For patients who develop ATV/r-induced renal stones, discontinuation of ATV/r is warranted because of the high risk of recurrence. Switching ATV/r to other antiretrovirals is warranted in those patients.

Atazanavir, equally to indinavir, causes urolithiasis, but both drugs have also been associated with CKD and fast declining eGFR in persons without clinical symptoms of urolithiasis, especially when the plasma drug concentration is boosted by concomitant ritonavir use [45].

It is not clear if unboosted atazanavir use (400 mg without ritonovir), known to induce lower plasma (and

urine?) atazanavir rate, is responsible for stones. In this case, the unboosted atazanavir can then be an alternative choice if the virological situation allows.

Thus, ATV/r should be carefully prescribed to patients with concomitant predisposing factors for renal stone formation or those with CKD. Healthcare professionals and patients should be informed that nephrolithiasis is a possible adverse event with the use of ATV/r.

Darunavir

In a cohort of HIV-infected individuals attending the Chelsea and Westminster Hospital Foundation Trust exposed to ATZ/r with those exposed to efavirenz (EFV)/ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted darunavir (DRV/r) over a 45-month study period, the rate of development of renal stones in the ATZ/r group compared with the EFV/LPV/r/DRV/r combined group was 7.3 (95% CI 4.7–10.8) per 1000 patient-years and 1.9 (95% CI 1.2–2.8) per 1000 patient-years ($P < 0.001$), respectively [34]. In a French study including 266 participants on stable (for an average of 22 months) antiretroviral therapy with 300 mg/day ATV/r, 400 mg/day unboosted atazanavir, boosted 800 or 1200 mg/day darunavir or 800 mg/day lopinavir/ritonavir (Kaletra), de Lastours *et al.* [37] found darunavir crystals in the urine of 7.8% (95% CI 0.4–15.2%) of patients treated with darunavir. The authors found that atazanavir—whether boosted or not—and boosted darunavir both resulted in significantly more drug crystals in urine compared with lopinavir; 7 patients (9%) taking atazanavir had measurable atazanavir crystals, while 4 people (8%) taking darunavir had detectable urine darunavir crystals. Darunavir, like atazanavir, concentrates highly in the urine of asymptomatic patients, which is not the case for lopinavir. The authors concluded that darunavir crystals were evidenced in the urine of a few asymptomatic patients receiving darunavir-based regimens [37]. Attention should be paid towards the potential renal toxicity of darunavir as well as atazanavir.

Other PIs

In contrast to indinavir and/or ATV/r, urolithiasis associated with other PIs, such as LPV/r, nelfinavir and amprenavir, is rare, and this could be due to the minimal (<3%) renal excretion of these PIs [46–49].

Engeler *et al.* [46] reported the first case of a nelfinavir urinary stone in a 37-year-old HIV-infected woman who had a medical history of intravenous drug abuse, hepatitis C virus coinfection and cervical intraepithelial neoplasia. The patient was treated for HIV infection for 15 years, initially with antiretroviral combination including indinavir then nelfinavir. Stone chemical composition revealed a content of 99% nelfinavir and 1% indinavir. Accordingly, the antiretroviral treatment was changed to fosamprenavir with ritonavir and delavirdine and 6 years later, the same patient experienced multiple bilateral obstructing stones. After retrieval, stone analysis revealed a composition of 95% unmodified amprenavir and 5% ritonavir [47]. Amprenavir is >90% metabolized in the liver. Excretion of unmodified amprenavir in urine and faeces is minimal (<1%).

Kidney stones attributable to poorly renal excreted saquinavir [49] and lopinavir [48] have also been reported in clinical cases. Lopinavir/ritonavir has been associated with seven cases of nephrolithiasis [48] but the stones were not analysed and so there is no proof that they contained lopinavir.

Non-PIs antiretroviral-based treatment

Several other antiretroviral drugs have been reported to cause urinary stones.

Raltegravir, a potent HIV-1 integrase strand transfer inhibitor, is eliminated in both urine (32%; raltegravir and its glucuronide, respectively, for 9 and 23%) and faeces (51%). The major mechanism for the clearance of raltegravir in humans is UGT1A1-mediated glucuronidation [50]. Only one case has been reported up to now [51]. This patient had a history of nephrolithiasis while on different treatment regimens (including tenofovir, emtricitabine, raltegravir, darunavir and ritonavir), although no obvious underlying metabolic or anatomical abnormality was identified. Stone fragments retrieved following lithotripsy consisted mainly of raltegravir. Plasma and urinary raltegravir concentrations were within normal limits, making the possibility of inadequate dosing unlikely. Such accumulation of raltegravir in the composition of urolithiasis should lead to the prescription of this compound only with caution in patients with urolithiasis history [51].

EFV is principally metabolized by the cytochrome P450 system to hydroxylated metabolites, with subsequent glucuronidation of these hydroxylated metabolites. Approximately 14–34% of an EFV dose was recovered in the urine and <1% of the dose was excreted as unchanged EFV. The co-administration of EFV and atazanavir in combination with ritonavir may lead to increased EFV exposure, which may worsen the tolerability profile of EFV [52] Two EFV urolithiasis cases up to now have been reported [53, 54]. In one of them, a 3-mm, radio-translucent, non-crystalline, beige stone was analysed. The drug crystals were birefringent needles. Stone analysis revealed a composition of EFV metabolites (60%) and unspecified proteins (40%) [54].

Contributing pro-lithogenic patient factors

Several factors may have influenced the occurrence of antiretroviral-associated urolithiasis.

Individual risk factors related to the patient and to the drugs are listed in Table 4 [55–58]. Patients with a history of urinary stones may have a higher risk for developing such complications while taking antiretroviral drugs. In one retrospective review, only 28% of indinavir-treated patients with nephrolithiasis had indinavir-containing stones. The other patients who were not taking indinavir had stones that contained calcium oxalate, ammonium acid urate and uric acid, and some had various metabolic abnormalities, including hypocitraturia, hyperoxaluria and hypercalciuria [22]. In addition, several other drugs commonly used in HIV-infected patients may have involved nephrolithiasis (Table 5). Recommended investigations for a patient who experienced urolithiasis are summarized in Table 6.

Prevention

Lithiasis formation depends on liquid intake, urinary pH, the quantity of crystals present in the urine and the persistence of crystalluria [58]. High urinary excretion, which favours urinary crystallization, is necessary for drugs to produce calculi [58]. Carriage of drug-containing urinary crystals is always abnormal and is estimated to lead in approximately two-thirds of all cases to lithiasis. In general, fluid intake should be increased to at least 2 L of water per

Table 4. Risk factors for drug-induced urinary calculi with a high risk for recurrent urolithiasis [55–58]

Patient-dependent risk factors
Personal or family history of urolithiasis
Pre-existing calculi
Residual stone fragments or bilateral vast stone burden
Obesity
Urinary stasis
Underlying lithogenic metabolic abnormalities (e.g. hypercalciuria, hypocitraturia, hyperuricaemia, including diabetes mellitus)
Underlying lithogenic diseases (hyperparathyroidism, cystinuria, primary hyperoxaluria; medullary sponge kidney, gastrointestinal malabsorption, ...)
Detoxification enzyme pattern
Abnormally low or high urine pH
Urinary tract infection
Low urine output
Environmental factors (e.g. hot temperature)
Drug-specific risk factors
High daily dose of drug
Long-standing treatment
High urinary excretion of the drug and/or its metabolites
Low aqueous solubility of the drug and/or its metabolites
Concomitant therapy that causes changes in the pharmacokinetics or metabolism of the drug
Size and morphology of drug crystals

Table 5. Drugs commonly used in HIV-infected patient involved in urolithiasis development

Therapeutic class	Drugs
Antibiotics	
Aminopenicillin	Ampicillin, amoxicillin
Cephalosporins	Ceftriaxone
Furanes	Nitrofurantoin
Quinolones	Norfloxacin, ciprofloxacin
Sulfonamides	Sulfamethoxazole, sulfadiazine
Antiviral	Acyclovir, foscarnet, ganciclovir
Xanthine oxidase inhibitors	Allopurinol

Table 6. Recommended routine laboratory investigation of urolithiasis

Serum
Creatinine, MDRD/CKD EPI creatinine clearance
Electrolytes: calcium, phosphate, magnesium
Urate
Parathyroid hormone and vitamin D levels
Urine (spot, 24-h urine collection)
Urinalysis, urinary pH
Culture and sensitivity
Electrolytes: sodium, calcium, phosphate, magnesium
Urate, oxalate, citrate, urea
Crystalluria
Low-dose renal CT scan
Stone composition analysis

day in patients without contraindications such as congestive heart failure or cirrhosis. There is good evidence from randomized trials that dietary modifications, including salt restriction, may also reduce recurrent stone formation [59]. Additional dietary modifications should be based on any biochemical abnormalities that are identified in the investigation of the cause of stone development [59]. In patients with low 24-h excretion of urinary citrate, prophylaxis with potassium citrate may be considered. When appropriate alternatives exist, other medications should be substituted in patients with medication-based urolithiasis. This strategy has been used in the management of indinavir-based stones with variable success [60]. Since most stones are radiolucent and are not detectable with plain radiographs, it is recommended that those patients be monitored (crystalluria) periodically during the first 6 months of therapy, then biannually thereafter for changes in renal function.

In conclusion, better awareness of the possible occurrence of lithogenic complications, and close surveillance of patients on long-term drug therapy with lithogenic potential should reduce the incidence of antiretroviral-induced nephrolithiasis.

Conflict of interest statement. None declared.

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