DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

A continuous publication, open access, peer-reviewed journal

ACCESS ONLINE

REVIEW

Renal effects of non-tenofovir antiretroviral therapy in patients living with HIV

Milena M McLaughlin PharmD, MSc[1,2], Aimee J Guerrero BS[1], Andrew Merker PharmD[1,3]

[1]Chicago College of Pharmacy, Midwestern University, 555 31st Street, Downers Grove, IL 60515, USA; [2]Northwestern Memorial Hospital, 251 E Huron St, Chicago, IL 60611, USA; [3]Mount Sinai Hospital, 1500 S Fairfield Ave, Chicago, IL 60608, USA

Abstract

A review of literature published regarding non-tenofovir antiretroviral agents causing renal adverse effects was conducted. The literature involving renal adverse effects and antiretroviral therapy is most robust with protease inhibitors, specifically atazanavir and indinavir, and includes reports of crystalluria, leukocyturia, nephritis, nephrolithiasis, nephropathy and urolithiasis. Several case reports describe potential nephropathy (including Fanconi syndrome) secondary to administration of abacavir, didanosine, lamivudine and stavudine. Case reports documented renal events such as acute renal failure, nephritis, proteinuria and renal stones with efavirenz administration. Regarding rilpivirine, a small increase of serum creatinine levels (SCr) was found in clinical trials; however, the clinical significance and impact on actual renal function is unknown. The integrase strand transfer inhibitors and enfuvirtide have a relatively safe renal profile, although studies have shown dolutegravir and raltegravir cause mild elevations in SCr without an impact on actual renal function. This is similar to the reaction observed with cobicistat, the pharmacokinetic enhancer frequently given with elvitegravir.

Keywords: anti-HIV agents, antiretroviral therapy, highly active, HIV infections, kidney, kidney diseases, nephrolithiasis, urolithiasis.

Citation

McLaughlin MM, Guerrero AJ, Merker A. Renal effects of non-tenofovir antiretroviral therapy in patients living with HIV. Drugs in Context 2018; 7: 212519. DOI: 10.7573/dic.212519

Introduction

The development and improved safety profile of antiretroviral therapy (ART) has allowed patients living with human immunodeficiency virus (HIV) to have a similar life expectancy to those not living with HIV [1]. However, comorbidities and ART may lead to renal injury [2]. The incidence of chronic kidney disease (CKD) in patients living with HIV (PLWH) ranges from 2 to 17% although the extent of renal injury depends on individual patient factors [3].

Although tenofovir disoproxil fumarate (TDF) is frequently considered as the antiretroviral most associated with renal adverse reactions, several other agents have potential renal adverse effects. These renal effects may include acute kidney injury (AKI), increased serum creatinine levels (SCr), reduced creatinine clearance (CrCl), reduced glomerular filtration rate (GFR), nephrolithiasis, urolithiasis, Fanconi syndrome, crystalluria, acute renal failure and progression to CKD [2]. Widely accepted mechanisms behind these renal insults are the inhibition of renal transporters and mitochondrial toxicities [4].

Although recently a preferred initial component of ART, atazanavir has been delegated to an alternate recommendation in part owing to the advancement of the integrase strand transfer inhibitors, which have better tolerability and no significant association with renal-related adverse events. Additionally, with the introduction of tenofovir alafenamide, the use of TDF is expected to decrease in exchange for the newer tenofovir salt. However, it is important to consider that in countries with decreased access to newer, more tolerable antiretroviral agents, many of the older agents more likely of inducing adverse renal events will be relied upon. With numerous antiretroviral agents available, clinicians must be aware of ART impact on potential renal issues. As many reviews of renal side effects focus on TDF, this will focus on non-TDF antiretrovirals.

Data search

An English language literature search from January 1996 through December 2016 was conducted via Medline. The search terms 'human immunodeficiency virus', 'HIV', 'Acquired

Immunodeficiency Syndrome', 'AIDS' and 'renal' (in addition to related medical subject heading [MeSH] terms) were used to identify articles detailing any type of renal injury related to ART. Any article detailing renal issues solely with TDF was excluded. Among the articles identified for review, the citations were reviewed for additional relevant references.

Nucleoside reverse transcriptase inhibitors (NRTIs)

Abacavir (ABC)

A prospective international cohort study used adult participants from the D:A:D study to investigate the correlation between using ART and the development of CKD in PLWH with normal renal function at baseline (estimated GFR [eGFR] >90 mL/min) [5]. After adjusting for confounding variables, cumulative exposure up to 6 years or more of ABC did not increase CKD incidence. A retrospective study found that patients with a history of hypertension (HR=2.39, $p<0.0001$) and acute renal injury (HR=2.40, $p<0.0001$) had an increased risk of developing CKD (defined as two consecutive eGFR [MDRD] ≤60 mL/min over ≥3 months) in addition to any ABC exposure (HR=1.37, $p=0.03$) within the previous 6 months [6].

Two case reports describe varying degrees of renal impairment with ABC use. One patient developed Fanconi syndrome with nephrogenic diabetes insipidus (NDI) [7]. The second case reported a male patient whose ART consisted of nelfinavir (NFV), lamivudine (3TC) and stavudine (d4T) before NFV was exchanged for ABC. The patient experienced flu-like symptoms, low grade fever, SCr increase (1.7–3.7 mg/dL) and malaise 5–7 days after switching to ABC. Biopsy found focal segmental glomerulosclerosis in 2 of 12 glomeruli without any evidence of HIV-associated nephropathy as well as acute interstitial nephritis consisting of clusters of eosinophils, which is indicative of drug-induced hypersensitivity reactions [8]. In both patients, ABC was discontinued and renal function returned to normal. It should be noted that hypersensitivity reactions have been reported within the first 4–6 weeks of the use of ABC. Common symptoms include fever, skin rash, fatigue, shortness of breath, cough, dyspnea and gastrointestinal (GI) issues. Patients may have these symptoms even if they have tested negative for the HLA B*5701 allele. It is recommended that ABC is discontinued and not rechallenged, as it could be life threatening [8].

Didanosine (ddI)

The development of Fanconi syndrome has been associated with ddI use in multiple reports. Three separate cases report patients treated with ddI presenting with metabolic disturbances, hyperuricemia, hypophosphatemia, glycosuria and elevated SCr levels. The first case confirmed the diagnosis of Fanconi syndrome when a biopsy revealed proximal tubular necrosis in addition to pancreatitis and NDI [9]. Interestingly, the patient in the second case had been on a long-term regimen that included ddI and 3TC [10]. The third case reported a diagnosis of NDI with polyuria polydipsia with large amounts of urinary phosphate excretion [11]. All symptoms of renal tubular dysfunction subsided once ddI therapy was discontinued. It is suggested that high ddI concentrations are associated with the development of NDI when coadministered with another antiretroviral [11]. The development of ddI-associated renal impairment has ranged from 19 months to 7 years from the cases reported in the literature. These varying time frames may be due to several factors including the interaction of other ART that was added or removed from the patient's regimen.

Lamivudine (3TC)

There have been multiple case reports of renal injury associated with ART including 3TC. One report describes two separate male patients who developed acute renal failure and pancreatitis. Blood urea nitrogen (BUN) and SCr level increased significantly in both cases (patient 1: 41.8 mmol/L and 760.2 µmol/L; patient 2: 38.2 mmol/L and 654.2 µmol/L) while receiving 3TC and full dose ritonavir (RTV) or saquinavir (SQV). Antiretroviral treatment was discontinued and when rechallenged, both patients presented with fever and worsening abdominal pain. Once ART was discontinued, all symptoms resolved and BUN/SCr levels normalized [12].

In a separate case report, a female patient developed Fanconi syndrome with lactic acidosis while on d4T and 3TC. Fanconi syndrome was attributed to injury of proximal renal tubular cells resulting from mitochondrial toxicity owing to ART [13]. Renal mitochondrial dysfunction was reported in another female patient that manifested into metabolic acidosis, elevated lactate levels, excessive urinary loss of bicarbonate and hypophosphatemia. This patient was also treated with 3TC and d4T for 13 months [14]. In each case, discontinuation of all ART improved all symptoms. These cases are further detailed in the stavudine section.

Stavudine (d4T)

Several case reports have associated d4T use with metabolic acidosis. One case describes a female PLWH who developed Fanconi syndrome and lactic acidosis while receiving d4T and 3TC for 9 months [13]. The patient was diagnosed with a high anion gap metabolic acidosis and her ART was subsequently discontinued. Proximal renal tubular injury was evident as there was a continued presence of glucose, phosphate and amino acids in the urine. The study authors concluded d4T was the likely cause as it is known to cause lactate levels to increase and mitochondrial DNA toxicity [13]. The combination of nucleoside analogues and protease inhibitors (PIs) may provoke pancreatorenal syndrome in PLWH. A male PLWH experienced severe abdominal pain and fever with continuous elevation of BUN and SCr levels [12]. The patient's regimen included d4T (80 mg daily), 3TC (300 mg daily) and RTV (1200 mg daily).

His symptoms began after the RTV dose was fully titrated. After developing metabolic acidosis, his ART was discontinued and dialysis was started. The authors noted that after resuming ART the symptoms returned [12]. This case is also detailed in the ritonavir section. A third case report described the incidence of lactic acidosis and renal failure secondary to acute hepatic failure in a patient on d4T and ddI for 18 months. The following laboratory parameters were taken on admission: lactate 139.2 mg/dL, bicarbonate 2.8, pH 7.02, SCr 1.38 mg/dL and BUN 35.9 mg/dL. Enlarged kidneys with perirenal effusion on both sides were revealed in a computed tomography (CT) scan performed on day 3. However, renal function parameters were normal. The patient fully recovered after intensive supportive care, 3 days of hemofiltration and ART discontinuation [15].

The following case report describes type B lactic acidosis in five different patients. All patients had been treated with d4T ranging from 7 to 12 months prior to hospital admission. Most patients complained of abdominal pain, nausea, vomiting and anorexia. CT scans revealed fatty liver disease in all five patients and pancreatitis in two patients. The mean peak lactate level was 10.3 mmol/L, and four of the five patients improved between 4 and 60 weeks. One died 24 days after hospital admission (serum lactate was 8.5 mmol/L), and an autopsy revealed acute pancreatitis with fat necrosis, massive hepatomegaly with fatty accumulation and acute renal tubular necrosis. Two patients received d4T monotherapy and the remaining patients were on d4T with either 3TC or zidovudine [16]. In another case report, a female had been treated with d4T and 3TC for 13 months. The patient developed metabolic acidosis (pH 7.17), hypophosphatemia (0.09 mmol/l) and presented with high levels of lactate (4.4. mmol/l). As the patient's serum lactate was elevated, it was suspected that mitochondrial toxicity was induced by the use of d4T or 3TC [14].

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Efavirenz (EFV)

Hypersensitivity reactions have been associated with the utilization of EFV. Several case reports have concluded that these reactions may have a negative impact on renal function. EFV was implicated as the cause of acute renal failure following a severe hypersensitivity reaction in a patient receiving TDF, 3TC, EFV and prophylactic doses of sulfamethoxazole/trimethoprim. Laboratory values and urinalysis revealed plasma SCr of 4.7 mg/dL, hypertransaminasemia, microhematuria, leukocyturia and granular casts present. The patient also developed severe hepatitis and pneumonitis but had no skin rashes or serum eosinophilia. TDF and 3TC were restarted and RTV replaced EFV with no incident [17]. Another case report described an event of acute interstitial nephritis in a male patient who had been treated with EFV, LPV/ritonavir (/r) and emtricitabine (FTC)/TDF for 5 years. The patient presented with a 4-day history of fever, anorexia, chest pain, reduced urinary output and mild diarrhea. Urinalysis revealed mild proteinuria and leukocytes in the urine. A renal biopsy showed acute interstitial nephritis with the presence of neutrophils and eosinophils. After treatment with prednisone and hemodialysis, the patient resumed treatment with LPV/r, nevirapine (NVP) and ABC/FTC with no complications [18].

The development of renal stones has also been attributed to EFV use in several case reports. The first report includes a male who developed pyelonephritis resulting from urinary obstruction. The patient presented with fever, chills and a 6-week history of left flank pain. EFV had been added to his regimen of ABC and 3TC 3 years prior. Laboratory parameters showed elevated C-reactive protein 180 mg/L, SCr 128 mmol/L, and leukocytes and bacteria in urine. The pyelonephritis led to septic shock and an emergency catheterization was performed, removing a 7-mm calculi composed of 50% EFV metabolites (M4, M5 and M8) and 50% unspecified proteins. Prior to the procedure SCr was 208 mmol/L and dropped to 112 mmol/l 4 days after. The patient resumed EFV treatment 6 months after remaining asymptomatic [19]. Continuation of efavirenz suggests that other factors may also have contributed to the development of the renal stone; this hypothesis is supported by the presence of 50% unspecified proteins upon stone analysis. Another report discusses a male patient with an 8-week duration of left flank pain while receiving EFV (600 mg), RTV (100 mg) and atazanavir (ATV; 300 mg) for the previous 2 years. The patient had a prior history of renal colic from unknown causes but reported no events for over 13 years owing to maintaining adequate hydration. SCr 166 mmol/L, C-reactive protein was 109 mg/dL and radiography showed calculi in both kidneys (3–4 mm and 1–2 mm). The patient spontaneously passed a 3-mm stone that was composed of 60% EFV and 40% unspecified proteins and the SCr levels dropped significantly 2 days later [20].

Although the use of EFV has been linked to the development of renal stones, data suggest that EFV carries a lower risk compared to ATV/r. A 45-month retrospective study in a large cohort compared the rate of developing renal stones between ATV/r (n=1000) versus a combined group of EFV, LPV/r, and darunavir (DRV)/r (n=3293). After adjusting for previous exposure to indinavir (IDV)/r exposure in each group, study authors concluded that exposure to ATZ/r carried a higher risk of developing renal stones compared to the EFV, LPV/r and DRV/r group cohort (5.67 *vs* 1.51 per 1000 patient years, respectively) [21]. This data is also detailed in the atazanavir section.

Barbour et al. reported a different type of renal impairment induced by EFV. In July 2004, a male patient presented to a renal clinic for elevated blood pressure and proteinuria. A 24-hour urine collection contained 8.1 g of protein and an ultrasound (US) showed cortical atrophy on both kidneys. Results from a renal biopsy confirmed focal interstitial fibrosis with no inflammation present with normal tubules and glomeruli. Months later EFV was discontinued owing to

nightmares and NVP (200 mg) was initiated. The proteinuria gradually decreased and normalized over 6 months. The presence of proteinuria is indicative of podocyte damage, which likely resulted from the use of EFV [22].

Rilpivirine (RPV)

The ECHO trial was a Phase III, randomized, double blind, active-controlled trial. It compared the efficacy, safety and tolerability of RPV (n=346) with EFV (n=344) in ART naïve PLWH. Both treatment group regimens also included TDF and FTC. There were no discontinuations in either treatment groups resulting from renal adverse events. Results revealed a small increase in the SCr level for the RPV group during the first treatment that remained stable over the remaining weeks. Estimated GFR levels were slightly below baseline as well, but were within normal limits. The study authors reaffirmed that RPV induced an increase in the SCr level, however, did not directly cause renal toxicity [23]. An analysis of the ECHO and THRIVE trial results compared the safety and efficacy of RPV (25 mg) with EFV (600 mg). There were no discontinuations of treatment related to renal adverse events. There was a small median increase in the SCr level in the RPV group (0.1 mg/dL) compared to EFV (0.01 mg/dL); however, the cystatin C levels did not show a decrease in GFR. This suggests that RPV inhibits the secretion of SCr and does not cause direct renal injury [24].

A study by Moss et al. investigated potential drug–drug interactions resulting from the inhibition or transport of RPV by various drug transporters [25]. RPV has the potential to impact substrates of ABCB1 transporter moving across the brush border membrane of proximal tubular cells in the kidney. Contrary to two separate efficacy studies reporting that a small increase in SCr level may have ensued from the inhibition renal proximal transporters by RPV, Moss et al. affirmed that it could not be explained by this mechanism [23–25]. However, the authors noted that SLC22A1 may contribute to variability in rilpivirine exposure, thereby affecting the interaction of rilpivirine with ABCB1 [25].

Integrase strand transfer inhibitors (INSTIs)

Dolutegravir (DTG)

Koteff et al. investigated the effects of DTG on SCr levels in 34 healthy patients over a 14-day period. The study was an open label, randomized, parallel, placebo-controlled study consisting of three different groups: DTG (50 mg daily), DTG (50 mg twice daily) and placebo (daily). Participants also received iohexol, which is freely filtered, and para-aminohippurate (PAH) on days 1, 7 and 14 to determine if DTG has an impact on glomerular filtration and renal blood flow. Additional GFR and tubular function biomarkers such as albumin, total protein and cystatin C were measured. The authors concluded that DTG (50 mg daily and twice daily) does not impact glomerular filtration or renal blood flow. They confirmed DTG may increase SCr levels by 10–14%. However, its effects are reversible and nonpathological [26]. Reese et al. investigated the metabolizing pathways and transporters involved in the distribution of DTG to determine potential drug–drug interactions. The study authors reported that DTG inhibits renal transporter OCT2, resulting in a mild increase in SCr that is reversible [27]. Eadon et al. subsequently reported that other specific biomarkers showed no evidence of renal injury [28]. Dolutegravir is eliminated (approximately 64%) in feces [29].

A single center, retrospective chart review assessed SCr and CrCl in newly diagnosed PLWH. Twenty-four patients were administered DTG and three or more SCr levels drawn within 60 weeks. The results confirmed that DTG increases the SCr levels initially but remains stable throughout the treatment. Only two patients on DTG had a decline in CrCl; however, the drug was not discontinued [30]. Small, nonprogressive increases in the SCr level were reported in the SPRING-1 trial [31]. In the SPRING-2 trial, 15 patients in the DTG group had grade 1–2 'treatment-emergent creatinine toxic effects' but no discontinuations were caused by renal events [32].

Elvitegravir (EVG)

When EVG is administered alone, it is metabolized by the liver into two metabolites. A clinical pharmacokinetic and pharmacodynamic study found 6.7% of radioactive EVG/RTV ([^{14}C]) was eliminated in the urine with no traces of unchanged parent drug observed in the urine. The study also concluded that 94.8% of the integrase inhibitor was eliminated in the feces via hepatobiliary excretion. These findings demonstrate that the metabolism and elimination profile of EVG will likely not affect PLWH that also have renal impairment [33]. As EVG is coadministered with cobicistat (COBI), it may be difficult to separate any adverse events occurring between these two agents. COBI is reviewed as an individual agent in its own section.

Raltegravir (RAL)

Two separate studies showed RAL is responsible for increased SCr levels without inducing renal injury. The first trial aimed to determine the renal effects of a 2-week, high dose regimen of RAL (0.2 mg/mL) in C57BL/6 mice. The study authors used 18 mice and categorized them into three different treatment groups: standard water, RAL-containing water (40 mg/kg/day) or DTG-containing water (2.7 mg/kg/day). The dose of RAL was determined by a previously published mouse model [34]. Both study groups were administered doses four times over the normal human dose of either integrase inhibitor and each mouse consumed an average 4.3 mL of water per day. Results confirmed that RAL significantly increases the SCr levels (0.25 mg/dL) compared

to control (0.17 mg/dL). The study authors concluded that there were no direct signs of nephrotoxicity and attributed the increase in the SCr level to the direct inhibition of renal OCT2 transporters [28]. The second trial was a single center, retrospective chart review that assessed SCr and CrCl in newly diagnosed PLWH. Twenty-nine patients were initiated on RAL and patients had a minimum of three SCr levels drawn within 60 weeks. Results revealed that RAL causes an initial increase in SCr levels that remains stable throughout the treatment [30].

Vassallo et al. provided the first case report of recurrent acute renal colic in a 25-year-old female living with HIV being treated with RAL, FTC/TDF, DRV and RTV. The patient had presented with right flank pain and a mild fever. A CT scan showed right obstructive kidney infection with an 8-mm kidney stone. Stone analysis revealed that it was primarily composed of RAL (269 µg/mg), along with RTV (23.1 µg/mg) and DRV (15.6 µg/mg). The plasma concentration and renal clearance of RAL were within normal limits, suggesting stone formation was not dose dependent [35]. Renal function was followed over a 12-week period in a renal transplant patient who was receiving RAL. The patient's CrCl steadily declined after starting RAL, 3TC and TDF (baseline: 62 mL/min, 12th week: 60 mL/min and follow up: 46 mL/min) [36]. Interestingly, another case reports a PLWH with normal renal function who developed acute renal failure while being treated with RAL and FTC/TDF. Three months prior to hospital admission, the patient's SCr level was 1 mg/dL. The patient complained of muscle pain in the dorsolumbar region, abdomen and neck. Dark urine, oliguria and elevated levels of phosphorus (7.23 mg/dL), AST (177 U/L) and ALT (196 U/L) were also found. The patient was given six sessions of hemodialysis, which improved his renal function and increased his diuresis. SCr was 1.8 mg/dL 16 days after admission and 1.1 mg/dL 21 days later. The renal injury was attributed to the development of rhabdomyolysis; however, the ART could have been directly responsible because the patient did not have any predisposing conditions [37]. Although tenofovir may have likely contributed to potential renal effects in these cases, raltegravir should be considered as an offending agent if all other causes of renal impairment have been excluded.

Contrary to previous trials, Gupta et al. reported that RAL can cause glomerular injury as this study found an increase in serum cystatin C and SCr levels. The 24-week long, single center, open-label, randomized trial consisted of 13 adult PLWH who remained on their current regimen of TDF/FTC/EFV and 15 patients who were switched to TDF/FTC and RAL. Renal function was estimated as CrCl (Cockcroft–Gault equation) and eGFR (cystatin C and cystatin C-creatinine). Results from the switch group showed significant decreases in CrCl at week 24 and reduction in eGFR estimates at week 8 that continued through week 24. Study authors noted that RAL reduces the plasma concentrations of TDF, indicating that renal impairments are likely produced by RAL [38]. It should also be considered that there may be an interaction between TDF renal toxicity and RAL use.

Protease inhibitors (PIs)

Amprenavir (AMP)

A single case report described a PLWH who developed a urinary stone secondary to AMP exposure. The patient had a history of urinary stones, having developed two stones composed of NFV (99%) and IDV (1%). The patient presented with right flank pain and recurrent urinary tract infections, and CT revealed five stones between the left and right kidneys. One stone was composed of 95% unmodified AMP and 5% RTV [39]. Surprisingly, no similar reports were found involving its prodrug formulation, fosamprenavir.

Atazanavir (ATV)

A relationship between urolithiasis and ATV administration has been well documented. Reports detail five patients who developed urolithiasis, four of which presented with typical renal colic symptoms (abdominal pain, nausea, vomiting and flank pain) and three were confirmed through imaging. ATV composition ranged from 41 to 100% in stone analysis from four patients [40–44]. ATV/r was reduced to 200/100 mg daily in the asymptomatic patient. No new stones were reported and HIV RNA remained undetectable [42]. Over a 5-year period, 30 cases of ATV-induced nephrolithiasis were reported in the Adverse Event Report System (AERS) of the Food and Drug Administration (FDA). Twelve cases reported stones composed of ATV with six cases including percent composition (40–100%). ATV was discontinued in 30% of cases [45]. ATV-associated urolithiasis was reported in 11 (0.97%) patients out of a review of 1134 patients. Four patients had a previous history of urolithiasis, and all patients had urolithiasis-associated symptoms. Stone composition ranged from 10 to 100% ATV [46]. A case–control comparison of 30 patients who developed nephrolithiasis (defined as stone composition containing ATV) following boosted or unboosted ATV administration and controls (n=90) who received boosted or unboosted ATV without associated nephrolithiasis was conducted. A history of IDV usage (44.8 *vs* 20%, p=0.02), urolithiasis secondary to IDV use (26.7 *vs* 1.2%, p=0.001) and a history of urolithiasis prior to ATV introduction (36.7 *vs* 7.8%, p=0.01) were more frequent in cases compared to controls. The median ATV stone composition was 89% (IQR 59.0–95%) [47].

In a retrospective study of 465 patients taking ATV/r and 775 patients taking other PIs, renal stone development was documented in a higher percentage of patients taking ATV (6.7%) compared to those taking other PIs (0.52%, hazard ratio [HR] 10.44, 95% CI: 3.685–29.59; p=0.001). Factors associated with stone formation were lower baseline eGFR (HR 1.189, 95% CI: 1.042–1.336; p=0.009) and higher baseline uric acid level (HR 1.334, 95% CI: 1.085–1.640; p=0.006) [48]. In a second retrospective cohort, the incidence of nephrolithiasis for patients on DRV/r (n=540) was compared to patients taking ATV/r (n=517). There were 37 (7.1%) patients taking ATV/r with nephrolithiasis compared to 1 (0.2%) of patients taking

DRV/r (HR 26.01, 95% CI: 3.541–191.0; p=0.001). ATV/r was found to have a significantly higher incidence (20.2 per 1000 patient years) of nephrolithiasis compared to DRV based regimens (0.86 per 1000 patient years) [49]. Another retrospective cohort compared the incidence of nephrolithiasis for ATV/r regimens (n=1206) compared to DRV/r, LPV/r and EFV based ART (n=4449). The rate of nephrolithiasis development for ATV/r was 7.3 per 1000 patient years (95% CI: 4.7–10.8) compared to 1.9 per 1000 patient years (95% CI: 1.2–2.8) for the DRV/r, LPV/r and EFV group (p=0.001) [21].

There are five case reports documenting ATV-induced crystalluria in patients receiving ATV/r 300/100 mg daily. Four patients experienced increased SCr levels (122–195% increase from baseline) with two patients developing tubulointerstitial nephritis (TIN) and another who eventually required hemodialysis. Two patients had confirmed crystals primarily composed (>60%) of ATV. ATV/r was discontinued in three cases resulting in either a stabilization or return to baseline of SCr level [50–54]. Another patient was diagnosed with TIN without crystalluria following presentation of weakness and lethargy after receiving ATV 400 mg daily for 4 weeks. There was a large increase in the SCr level (1.4–11.1 mg/L) and renal biopsy showed TIN with no obstruction found. ATV was discontinued and renal function returned to baseline [55].

Studies have also assessed ATV plasma levels and incidence of nephrotoxicity or urolithiasis. During a study of 98 patients, nine (9.18%) experienced renal colic and six of these had urinary crystals with three composed of ATV. The mean ATV level for those with urolithiasis was slightly higher (1303 *vs* 1161 mg/L) but did not reach statistical significance. Twelve patients (16.2%) met criteria for renal failure (eGFR <60 mL/min or eGFR decrease of 20 mL/min) and higher ATV plasma levels were not associated with renal failure [56]. Studies were conducted involving potential single nucleotide polymorphisms (SNPs) associated with ATV metabolism. In those who received boosted or unboosted ATV and developed urolithiasis, there was an association of SNPs at three different locations with an increased incidence of urolithiasis compared to controls. Only patients of Japanese and East Asian descent were enrolled. The authors commented that the allele variant studied is more common in those of African and European origin based on previous gene mapping, indicating the possibility that ATV-induced nephrolithiasis may be more common in those patients [57].

ATV plasma and urine levels were collected in patients receiving either ATV 400 mg or ATV/r 300/100 mg in asymptomatic patients. The median ATV urine level was significantly higher than median plasma level for ATV 400 mg (14.3 mg/L, range 0.15–50.5 *vs* 0.5 mg/L, range 0.1–11.5 mg/L; p=0.001) and ATV/r 300/100 mg (22.3 mg/L, range 0.25–99.0 *vs* 1.3 mg/L, range 0.2–4.3 mg/L, respectively; p=0.001). Among the 78 patients receiving ATV, 8.9% (95% CI: 2.6–15.2) had crystals composed of ATV. All had received ATV/r. Duration of ATV therapy was the only factor associated with ATV crystals (p=0.044) [58].

Two case reports have documented AKI secondary to ATV administration. One patient had no baseline renal impairment (SCr 1.14 mg/dL) and was receiving ATV/r 300/100 mg while the other patient had baseline renal impairment (SCr 2.0 mg/dL) and was treated with ATV 400 mg daily. After receiving ATV for several weeks, both patients experienced a doubling of SCr level, at which point ATV was discontinued and the SCr level returned to normal [59,60].

Numerous studies have shown a potential impact of ATV on CKD progression. One study assessed patients taking either ATV 400 mg (n=189) or ATV/r 300/100 mg (n=180) daily with baseline eGFR (using MDRD) >50 mL/min. After 144 weeks of therapy, no significant change in eGFR was observed between groups (p=0.4297) with a similar decrease for ATV (29%) and ATV/r (28%) [61]. A large prospective study followed patients from ART initiation until CKD progression (eGFR <60 mL/min/1.73 m^2 using Cockcroft–Gault or >25% decline if baseline eGFR <60 mL/min/1.73 m^2). For each additional year of ATV exposure, there was a 22% increased incidence rate ratio (IRR 1.21, 95% CI: 1.09–1.34; p=0.003) in CKD progression [62]. In a large retrospective study assessing CKD progression (eGFR <60 mL/min/1.73 m^2 using Cockcroft–Gault) in those with baseline eGFR >90 mL/min/1.73 m^2, ATV/r was found to have a 20% increased incidence to CKD progression with each additional year of exposure (aIRR 1.20, 95% CI: 1.13–1.26; p=0.0001). With 5 years of ATV/r exposure, the incidence doubled (IRR 2.44, 95% CI: 1.86–3.21; p=0.0001) [5]. ATV/r was associated with an increased incidence of eGFR <70 mL/min (aIRR 1.19/year, 95% CI: 1.09–1.32/year) but not eGFR <60 mL/min (aIRR 1.14/year, 95% CI: 0.93–1.39/year) in patients receiving ART with baseline eGFR >90 mL/min/1.73 m^2 (using Cockcroft–Gault) [63]. The REMAIN study observed adult, treatment-naïve PLWH starting a regimen including ATV/r. During follow up, there was a nonsignificant mean change in eGFR after 5 years of therapy (–1.3 mL/min, 95% CI: –30.3–27.8 mL/min) with a 2.6% incidence of progressing to eGFR < 60 mL/min [64]. This incidence of CKD progression to eGFR < 60 mL/min is similar to that previous studies found for patients receiving any ART (0.6–3.3%) [5,62,63].

One proposed mechanism for ATV-associated AKI or TIN is ATV-induced leukocyturia. However, a retrospective study assessing patients on boosted or unboosted ATV (n=105, baseline eGFR using CKD-EPI: 112.6 mL/min/1.73 m^2) found no patients with leukocyturia (defined as WBC >5 cells) at last assessment. Patients were followed over a median of 421 days (range 208–914). Five patients with leukocyturia at baseline had less than 5 WBCs at last assessment. There was no significant decrease in eGFR (–0.3187 mL/min/1.73 m^2, p=0.689) [65]. Patients with stable HIV disease (n=49, undetectable viral load and CD4 >200 cells/mm^3) who were receiving either ATV or ATV/r had ATV plasma levels obtained to assess any association with ATV and renal function. Although the ATV level was significantly higher in patients receiving ATV/r (1438 ± 1287 mg/L) compared to ATV alone (612 ± 600 mg/L, p=0.028), there was no difference in renal function [66].

Darunavir (DRV)

The literature describing impact of DRV on renal-related adverse effects is sparse. DRV urine concentrations and crystal formation was assessed in a study of patients receiving DRV/r 800/100 mg (n=98) daily or 1200/200 mg (n=25) total daily dose. DRV levels were approximately 13 times more concentrated in the urine compared to plasma. The median urine and plasma concentration for patients on DRV/r 800/100 mg (2.35 mg/L, range 0.1–12.5 and 26.9 mg/L, range 0.6–112 mg/L, respectively) and DRV/r 1200/200 mg total daily dose (3.69 mg/L, range 0.08–11.3 and 29.7 mg/L, range 0.53–182 mg/L, respectively) were similar. Urine crystal analysis was performed on 51 patients between the DRV/r dosing regimens, and only four patients (three on DRV/r 800/100 mg) had crystals containing DRV (7.8%, CI: 0.4–15.2). There was no significant difference for DRV plasma and urine levels, duration of DRV treatment or urine pH for patients who developed crystals and those who did not [58].

Indinavir (IDV)

IDV has an extensive history of renal-related adverse effects ranging from urolithiasis to CKD progression. A retrospective study of patients who received IDV found 7.3% had a renal-related event. These events included loin pain (58%), renal colic (42%) and dysuria with either loin pain or renal colic (19%). Elevated SCr levels (>1.35 mg/dL) were found in 19% of patients with loin pain and 22% with renal colic. Potential precipitating events were documented in 26% of patients, including fluid depletion or dose increase. The only risk factor associated with an increased risk of renal events was concurrent acyclovir use (OR 1.99, 95% CI: 1.14–3.51; p=0.016) [67]. Another study attempted to seek potential risk factors for urological symptoms with IDV use. Patients receiving IDV (n=644) were compared to those receiving a different PI (n=1219). Urological symptoms were experienced in 9% of patients receiving IDV compared to 4% on a different PI (RR 8.7, 95% CI: 7.4–10.2). Lean body mass less than 68 kg, HIV RNA less than 1000 copies/mL, absence of co-trimoxazole use and previous change of ART secondary to intolerance were associated with urologic symptoms [68].

IDV plasma samples obtained in patients with urological symptoms were compared to controls without symptoms. Among those with symptoms, 80% had a level higher than the upper 95% confidence limit for controls. The mean ratio IDV plasma concentration for symptomatic patients to controls was significantly higher (2.64, 95% CI: 1.68–4.14; p=0.05) [69]. One study found by simulating the environment within the descending Loop of Henle (pH 7.4, temperature 37°C), a plasma IDV concentration of 6.4 mg/L was needed to precipitate IDV crystallization [70].

Two prospective studies assessed the presence of leukocyturia (defined as >75 cells/µL) in adults (n=184) and children (n=30) receiving IDV. Leukocyturia was experienced in 35% of adults and 53% of children, while persistent leukocyturia (defined as two separate episodes of leukocyturia) was found in 24% of adults and 37% of children. C_{max} higher than 9 mg/L for adults was associated with higher risk of persistent leukocyturia (RR 2.5, 95% CI: 1.1–5.8) [71,72]. Adult patients with a median IDV plasma level of at least 9 mg/L had a RR 2.5 (95% CI: 1.1–5.8 mg/L) to experience persistent leukocyturia [71].

One retrospective study followed 240 patients receiving IDV, of which 19 (7.9%) had symptoms of either nephrolithiasis with flank pain, flank pain with no renal stones or dysuria and urinary frequency. Among these, 16 had a urinalysis with all samples having IDV crystals confirmed. Asymptomatic IDV crystalluria was found in 20% of these patients [73]. Another study followed IDV treated patients (n=54) without renal manifestations. During 1 year of observation, 66.6% developed IDV crystalluria and 24% of the 579 samples collected contained IDV crystals [74]. Several case reports and studies illustrate the association between IDV and urolithiasis. Two case reports describe IDV-associated crystalluria [75,76]. A multitude of patients from these reports presented with flank pain and had stones or crystals in the urine [77–86].

There are seven studies assessing the development of renal colic in patients receiving IDV. These studies included patients (n=2557; range 79–758) who were receiving IDV 800 mg twice or three times daily. Between the studies, 350 patients experienced renal colic (13.6%, range 4–28.4%) [87–93]. Three studies analyzed a total of 15 stones for IDV composition, of which three returned with IDV [88,91,92]. IDV discontinuation was documented in three studies (n=153, range 7–96) [88,90,91]. The incidence of renal colic was correlated with increasing environmental temperature as observed during warmer months (r=0.894, p=0.0001) [90].

Case reports detail 15 patients (16–60 years old) receiving IDV (doses ranging from 800 mg three times weekly to 2400 mg three times daily) who experienced suspected IDV-associated nephropathy. Thirteen patients experienced increased SCr levels from baseline, with elevations 140–335% [94–103]. Nine patients had renal biopsies performed, two of which had evidence of sclerotic glomeruli, two described tubular atrophy and all had crystals present in either the collecting ducts and/or tubules [95,97,98,100–103]. Four other patients had nephropathy confirmed through either pyelogram or renal US that revealed renal atrophy [96,104,105]. One patient was diagnosed with nephropathy owing to increasing SCr (1.2–1.7 mg/dL after 3 months of IDV) and eosinophils in the urine [94]. Another patient with an increasing SCr level, hematuria, pyuria and proteinuria had an unremarkable renal US. IDV was discontinued with resolution of elevated SCr level, and the patient declined renal biopsy and eventually was rechallenged with IDV which resulted in similar adverse events and led to permanent IDV discontinuation [98]. IDV was documented as discontinued in 12 patients, with SCr levels returning to baseline or near baseline in the nine patients where baseline values were reported [94–99,102–104]. A retrospective study included patients on either IDV (n=32), IDV/r (n=25) or SQV/r (n=54) and the development of nephropathy. Patients taking IDV experienced a significant elevation in mean (SD) SCr level from baseline

(0.97 ± 0.17 to 1.05 ± 0.24 mg/dL, p=0.019) [106]. Another retrospective study followed patients receiving IDV (n=671) who developed interstitial nephritis (defined as pyuria with either an elevated SCr level from baseline or presence of urinary casts). A total of 14 patients (2%) met criteria and IDV was discontinued in 13 patients, with pyuria resolving in all cases [107].

Two case reports detail patients that developed an AKI secondary to a urinary obstruction from IDV [108,109]. One retrospective study reviewed patients receiving IDV (n=232) who developed a renal event (defined as SCr over 1.2 mg/dL or 50% increase from baseline). Thirty-three (14%) patients had a renal event [110]. A prospective study followed patients for up to 24 months and receiving IDV (n=555) with the endpoint being a 50% increase in SCr level from baseline. Thirty-five patients (6.3%) met this endpoint [91].

Several studies describe the use of IDV and CKD progression. Patients receiving IDV 2400 mg/day (n=106) were compared to those receiving either RTV (n=31) or NFV (n=30) for a SCr level elevation of 20% from baseline. Twenty (18.6%) of IDV patients developed a 20% elevation [111]. A retrospective review of PLWH receiving ART (n=7378) were followed to assess CKD progression (two consecutive measurements of eGFR ≤ 60 mL/min/1.73 m^2 using MDRD). Recent exposure to IDV was found to be associated with an increased risk for CKD (HR 2.03, 95% CI: 1.42–2.90; p=0.0001) [6]. Another large retrospective study assessed patients receiving ART (n=6843) including IDV (n=3156) and CKD progression (defined as eGFR ≤ 60 mL/min/1.73 m^2 twice and being 3 months apart or for baseline eGFR ≤ 60 mL/min/1.73 m^2 a 25% decline from baseline; eGFR calculated using Cockcroft–Gault). Patients had a 11% increased incidence of CKD progression for each additional year of IDV exposure (p=0.05) [62]. An additional study found patients receiving IDV had a significant mean decrease from baseline eGFR (mL/min/1.73 m^2, using MDRD) for those with a baseline eGFR ≥ 90 mL/min/1.73 m^2 (–3.29, 95% CI: –5.25 to –1.32) and baseline eGFR ≤ 90 mL/min/1.73 m^2 (–2.14, 95% CI: –3.63 to –0.64) [112].

Lopinavir/ritonavir (LPV/r)

A case series of patients who received LPV/r and developed renal colic was reported. Urolithiasis was confirmed through imaging for all patients. Two patients had a history of urolithiasis secondary to IDV therapy. Urolithiasis resolved for two patients without therapy modification [113]. When comparing the cumulative incidence of urinary stones for patients on LPV/r, EFV or DRV/r (5.4 urinary stones per 1000 patients, 95% CI: 3.2–7.6), there was a significantly lower risk of stone formation compared to ATV/r (20 urinary stones per 1000 patients, 95% CI: 13–30; p=0.001) [21]. A study reported two patients on LPV/r developing urinary crystals; however, they were primarily composed of calcium monohydrate and dehydrate [58].

There are several studies showing a potential link of LPV/r and CKD progression. A large study of 6843 patients receiving ART were followed until confirmed CKD progression (eGFR <60 mL/min/1.73 m^2 using Cockcroft–Gault or >25% decline if baseline eGFR <60 mL/min/1.73 m^2). LPV/r had a significant increase in CKD progression with each additional year of exposure (8%, p=0.05) but was lower compared to other agents with significant progression (TDF 16%, IDV 11% and ATV 22%). The increase in CKD progression for LPV/r patients was only significant after 36 months of exposure [62]. Cumulative LPV/r exposure was a significant indicator for progression to eGFR <70 mL/min (adjusted incidence rate ratio [aIRR] 1.11/year, 95% CI: 1.05–1.17) and eGFR <60 mL/min (aIRR 1.2/year, 95% CI: 1.16–1.28) in a study of 22,603 patients [63]. An additional study determined LPV/r had a significantly increased risk of CKD progression (IRR 1.11 per year, 95% CI: 1.06–1.16; p=0.0001) and was independent of concurrent TDF administration [5].

Nelfinavir (NFV)

There are two published case reports documenting NFV and renal-related adverse effects. One involved a patient receiving NFV who was previously on IDV presenting with right flank pain and hematuria. Renal US revealed right-sided nephrolithiasis and the patient received extracorporeal shock wave lithotripsy (ESWL). Symptoms resolved but returned 6 months later. ESWL was performed again and stone analysis showed a composition of NFV (99%) and IDV (1%) [114]. Another patient presented with asymptomatic AKI (SCr 0.9 mg/dL at baseline, 3.2 mg/dL on presentation). Renal US was unremarkable and kidney biopsy demonstrated tubules with intraluminal deposits and chronic TIN. Crystals were obtained and analyzed, of which the molecular weight was consistent with the molecular weight of NFV free base [48].

Ritonavir (RTV)

There are several case reports describing nine patients who experienced AKI shortly after initiation of RTV at treatment doses (total daily dose ranged from 600 to 1200 mg). The percent SCr level increase compared to baseline ranged from 41 to 591%. RTV was discontinued in all patients, which resulted to a return of baseline SCr level in each patient [12,115–118]. One patient had developed pancreatorenal syndrome and the patient received hemodialysis for 16 days and the SCr level returned to baseline [12].

A retrospective study followed patients who received RTV 1200 mg daily (n=87) to assess the incidence of renal insufficiency (50% SCr level increase from baseline). Twelve patients met renal insufficiency criteria after starting RTV, with a median SCr level increase of 66% (range 51–242%). These 12 patients had a median eGFR decrease of 46 mL/min (range 21–96 mL/min); however, 10 had risk factors for SCr level elevations (sepsis, nephrotoxic agents, dehydration) [119].

Saquinavir (SQV)

A case report described hematuria and renal stones in a patient receiving SQV 600 mg three times daily for several months.

The patient continued to experience symptoms with renal stones identified on multiple occasions. SQV was eventually discontinued with no report of renal colic over the next year [120]. Another patient received SQV 1800 mg daily and developed pancreatitis and elevated SCr level (3.7 mg/dL) which increased over several days (peaked at 7.4 mg/dL). SQV was discontinued and all values returned to normal 1 month after hospital discharge [12].

Fusion inhibitor

Enfuvirtide (T20)

The T20 versus Optimized Regimen Only Study 1 (TORO 1) studied T20 when incorporated as a part of a three to five antiretroviral regimen in patients with multidrug resistant HIV-1 infection. Among 491 patients that received at least one dose of the fusion inhibitor, there was one patient that developed membranoproliferative glomerulonephritis 57 days after initiating treatment with T20, as part of a regimen consisting of TDF, 3TC, LPV/r, AMP and EFV. This patient had a past medical history of proteinuria, hematuria and diabetes. This treatment regimen was rechallenged on day 223 and the patient suffered a severe respiratory response with no increase in eosinophils from baseline [121]. Of note, no reports of renal injury with maraviroc were found.

Pharmacokinetic enhancer

Cobicistat (COBI)

Two studies of COBI investigated the safety and efficacy in patients with mild/moderate renal function. One study evaluated the effects of estimated GFR and actual GFR in mild/moderate renal function of otherwise healthy volunteers when receiving COBI (150 mg daily) only (n=18) [122]. The second study investigated patients switched from RTV to COBI in combination with either ATV or DRV (n=73) [123]. Both trials reported that participants on COBI had a small increase in SCr levels within the first week; however, this normalized once COBI was discontinued. McDonald et al. reported that there were three patients for whom SCr levels increased ≥ 0.4 mg/dL from baseline. However, no tubular abnormalities were associated with the increase and they continued receiving COBI [123]. As COBI does inhibit MATE1, a cationic renal transporter, this causes an increased SCr and decreased eGFR [122].

Conclusion

There is a variety of potential renal-related adverse effects that may occur with non-TDF antiretroviral agents that are important to consider when initiating ART. These effects may include crystalluria, leukocyturia, nephritis, nephrolithiasis, nephropathy, renal colic and urolithiasis. The majority of literature available detailing renal impact of NRTIs, NNRTIs and INSTIs primarily involve case reports. Outside of TDF, ATV and IDV have the most available literature outlining a diverse range of renal-related adverse effects and use is cautioned in those already with existing renal-related disease. Although many of these drugs are no longer recommended per some guidelines (e.g. US guidelines), past use of these agents may be relevant when assessing a patient for renal injury and certain patient populations may not have access to all agents.

Disclosure and potential conflicts of interest: The authors report no conflicts of interest. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at http://www.drugsincontext.com/wp-content/uploads/2018/02/dic.212519-COI.pdf

Funding declaration: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Article URL: http://www.drugsincontext.com/renal-effects-of-non-tenofovir-antiretroviral-therapy-in-patients-living-with-hiv

Correspondence: Milena McLaughlin, PharmD, MSc, Midwestern University Chicago College of Pharmacy, Department of Pharmacy Practice, 555 31st St., Downers Grove, IL, 60515, USA. mmclau@midwestern.edu

Provenance: invited; externally peer reviewed.

Submitted: 1 December 2017; **Peer review comments to author:** 15 January 2018; **Revised manuscript received:** 22 February 2018; **Accepted:** 22 February 2018; **Publication date:** 21 March 2018.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252772009.

For all manuscript and submissions enquiries, contact the Editorial office dic.editorial@bioexcelpublishing.com

For all permissions, rights and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. May MT, Gompels M, Delpech V, Porter K, Orkin C, Kegg S, Hay P, Johnson M, Palfreeman A, Gilson R, Chadwick D, Martin F, Hill T, Walsh J, Post F, Fisher M, Ainsworth J, Jose S, Leen C, Nelson M, Anderson J, Sabin C, Study UKCHC. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. AIDS. 2014;28(8):1193–202. http://dx.doi.org/10.1097/QAD.0000000000000243
2. Gupta SK, Eustace JA, Winston JA, Boydstun, II, Ahuja TS, Rodriguez RA, Tashima KT, Roland M, Franceschini N, Palella FJ, Lennox JL, Klotman PE, Nachman SA, Hall SD, Szczech LA. Guidelines for the management of chronic kidney disease in HIV-infected patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2005;40(11):1559–85. http://dx.doi.org/10.1086/430257
3. Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. Nephrol Dial Transplant. 2017;32(3):434–9. http://dx.doi.org/10.1093/ndt/gfw064
4. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. Am J Kidney Dis. 2005;45(5):804–17. https://dx.doi.org/10.1053/j.ajkd.2005.02.010
5. Mocroft A, Lundgren JD, Ross M, Fux CA, Reiss P, Moranne O, Morlat P, Monforte A, Kirk O, Ryom L. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: A prospective international cohort study. Lancet HIV. 2016;3(1):e23–32. http://dx.doi.org/10.1016/s2352-3018(15)00211-8
6. Flandre P, Pugliese P, Cuzin L, Bagnis CI, Tack I, Cabie A, Poizot-Martin I, Katlama C, Brunet-Francois C, Yazdanpanah Y, Dellamonica P. Risk factors of chronic kidney disease in HIV-infected patients. Clin J Am Soc Nephrol. 2011;6(7):1700–7. http://dx.doi.org/10.2215/cjn.09191010
7. Ahmad M. Abacavir-induced reversible Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome. J Postgrad Med. 2006;52(4):296–7. http://www.jpgmonline.com/text.asp?2006/52/4/296/28158
8. Krishnan M, Nair R, Haas M, Atta MG. Acute renal failure in an HIV-positive 50-year-old man. Am J Kidney Dis. 2000;36(5):1075–8. https://doi.org/10.1053/ajkd.2000.19114
9. Crowther MA, Callaghan W, Hodsman AB, Mackie ID. Dideoxyinosine-associated nephrotoxicity. AIDS. 1993;7(1):131–2.
10. Izzedine H, Launay-Vacher V, Deray G. Fanconi syndrome associated with didanosine therapy. AIDS. 2005;19(8):844–5.
11. D'Ythurbide G, Goujard C, Mechai F, Blanc A, Charpentier B, Snanoudj R. Fanconi syndrome and nephrogenic diabetes insipidus associated with didanosine therapy in HIV infection: A case report and literature review. Nephrol Dial Transplant. 2007;22(12):3656–9. http://dx.doi.org/10.1093/ndt/gfm467
12. Stricker RB, Man KM, Bouvier DB, Goldberg DA, Mendiola AE. Pancreatorenal syndrome associated with combination antiretroviral therapy in HIV infection. Lancet. 1997;349(9067):1745–6. http://dx.doi.org/10.1016/s0140-6736(05)62957-1
13. Nelson M, Azwa A, Sokwala A, Harania RS, Stebbing J. Fanconi syndrome and lactic acidosis associated with stavudine and lamivudine therapy. AIDS. 2008;22(11):1374–6. http://dx.doi.org/10.1097/QAD.0b013e328303be50
14. Morris AA, Baudouin SV, Snow MH. Renal tubular acidosis and hypophosphataemia after treatment with nucleoside reverse transcriptase inhibitors. AIDS. 2001;15(1):140–1.
15. Koch RO, Graziadei IW, Zangerle R, Romani N, Maier H, Vogel W. Acute hepatic failure and lactate acidosis associated with antiretroviral treatment for HIV. Wien Klin Wochenschr. 2003;115(3–4):135–40.
16. Mokrzycki MH, Harris C, May H, Laut J, Palmisano J. Lactic acidosis associated with stavudine administration: A report of five cases. Clin Infect Dis. 2000;30(1):198–200. http://dx.doi.org/10.1086/313594
17. Angel-Moreno-Maroto A, Suarez-Castellano L, Hernandez-Cabrera M, Perez-Arellano JL. Severe efavirenz-induced hypersensitivity syndrome (not-DRESS) with acute renal failure. J Infect. 2006;52(2):e39–40. http://dx.doi.org/10.1016/j.jinf.2005.05.020
18. Curry E, Thomas M, Yehia M. Renal impairment and hypersensitivity reaction due to efavirenz. Nephrology (Carlton). 2008;13(6):541. http://dx.doi.org/10.1111/j.1440-1797.2008.00968.x
19. Wirth GJ, Teuscher J, Graf JD, Iselin CE. Efavirenz-induced urolithiasis. Urol Res. 2006;34(4):288–9. http://dx.doi.org/10.1007/s00240-006-0052-6
20. Izzedine H, Valantin MA, Daudon M, Mohand HA, Caby F, Katlama C. Efavirenz urolithiasis. AIDS. 2007;21(14):1992. http://dx.doi.org/10.1097/QAD.0b013e3282ef792f
21. Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. AIDS. 2011;25(13):1671–3. http://dx.doi.org/10.1097/QAD.0b013e32834a1cd6
22. Barbour TD, Furlong TJ, Finlayson RJ. Efavirenz-associated podocyte damage. AIDS. 2007;21(2):257–8. http://dx.doi.org/10.1097/QAD.0b013e32801120d1
23. Molina JM, Cahn P, Grinsztejn B, Lazzarin A, Mills A, Saag M, Supparatpinyo K, Walmsley S, Crauwels H, Rimsky LT, Vanveggel S, Boven K. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO):

A phase 3 randomised double-blind active-controlled trial. Lancet. 2011;378(9787):238–46. http://dx.doi.org/10.1016/s0140-6736(11)60936-7
24. Cohen CJ, Molina JM, Cassetti I, Chetchotisakd P, Lazzarin A, Orkin C, Rhame F, Stellbrink HJ, Li T, Crauwels H, Rimsky L, Vanveggel S, Williams P, Boven K. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. AIDS. 2013;27(6):939–50. http://dx.doi.org/10.1097/QAD.0b013e32835cee6e
25. Moss DM, Liptrott NJ, Curley P, Siccardi M, Back DJ, Owen A. Rilpivirine inhibits drug transporters ABCB1, slc22a1, and slc22a2 in vitro. Antimicrob Agents Chemother. 2013;57(11):5612–8. http://dx.doi.org/10.1128/aac.01421-13
26. Koteff J, Borland J, Chen S, Song I, Peppercorn A, Koshiba T, Cannon C, Muster H, Piscitelli SC. A Phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol. 2013;75(4):990–6. http://dx.doi.org/10.1111/j.1365-2125.2012.04440.x
27. Reese MJ, Savina PM, Generaux GT, Tracey H, Humphreys JE, Kanaoka E, Webster LO, Harmon KA, Clarke JD, Polli JW. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. Drug Metab Dispos. 2013;41(2):353–61. http://dx.doi.org/10.1124/dmd.112.048918
28. Eadon MT, Zhang H, Skaar TC, Hato T, Dagher PC, Gupta SK, Desta Z. A two-week regimen of high-dose integrase inhibitors does not cause nephrotoxicity in mice. Antivir Chem Chemother. 2015;24(2):72–6. http://dx.doi.org/10.1177/2040206615595318
29. Castellino S, Moss L, Wagner D, Borland J, Song I, Chen S, Lou Y, Min SS, Goljer I, Culp A, Piscitelli SC, Savina PM. Metabolism, excretion, and mass balance of the HIV-1 integrase inhibitor dolutegravir in humans. Antimicrob Agents Chemother. 2013;57(8):3536–46. http://dx.doi.org/10.1128/AAC.00292-13
30. Lindeman TA, Duggan JM, Sahloff EG. Evaluation of serum creatinine changes with integrase inhibitor use in human immunodeficiency virus-1 infected adults. Open Forum Infect Dis. 2016;3(2):ofw053. http://dx.doi.org/10.1093/ofid/ofw053
31. Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, Almond S, St Clair M, Flack N, Min S. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS. 2013;27(11):1771–8. http://dx.doi.org/10.1097/QAD.0b013e3283612419
32. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, Baril JG, Domingo P, Brennan C, Almond S, Min S. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;13(11):927–35. http://dx.doi.org/10.1016/s1473-3099(13)70257-3
33. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. Clin Pharmacokinet. 2011;50(4):229–44. http://dx.doi.org/10.2165/11584570-000000000-00000
34. Beck-Engeser GB, Eilat D, Harrer T, Jack HM, Wabl M. Early onset of autoimmune disease by the retroviral integrase inhibitor raltegravir. Proc Natl Acad Sci U S A. 2009;106(49):20865–70. http://dx.doi.org/10.1073/pnas.0908074106
35. Vassallo M, Dunais B, Naqvi A, Garaffo R, Durant J. Raltegravir-induced nephrolithiasis: A case report. AIDS. 2012;26(10):1323–4. http://dx.doi.org/10.1097/QAD.0b013e328353fda1
36. Moreno A, Perez-Elias MJ, Casado JL, Fortun J, Barcena R, Quereda C, Del Campo S, Gutierrez C, Pastor O, Nuno J, Fernandez A, Moreno S. Raltegravir-based highly active antiretroviral therapy has beneficial effects on the renal function of human immunodeficiency virus-infected patients after solid organ transplantation. Liver Transpl. 2010;16(4):530–2. http://dx.doi.org/10.1002/lt.22005
37. Masia M, Enriquez R, Sirvent A, Gutierrez F. Severe acute renal failure associated with rhabdomyolysis during treatment with raltegravir. A call for caution. J Infect. 2010;61(2):189–90. http://dx.doi.org/10.1016/j.jinf.2010.04.011
38. Gupta SK, Mi D, Moe SM, Dube MP, Liu Z. Effects of switching from efavirenz to raltegravir on endothelial function, bone mineral metabolism, inflammation, and renal function: A randomized, controlled trial. J Acquir Immune Defic Syndr. 2013;64(3):279–83. https://doi.org/10.1097/QAI.0b013e3182a97c39
39. Feicke A, Rentsch KM, Oertle D, Strebel RT. Same patient, new stone composition: Amprenavir urinary stone. Antivir Ther. 2008;13(5):733–4. https://doi.org/10.5167/uzh-4758
40. Anderson PL, Lichtenstein KA, Gerig NE, Kiser JJ, Bushman LR. Atazanavir-containing renal calculi in an HIV-infected patient. AIDS. 2007;21(8):1060–2. http://dx.doi.org/10.1097/QAD.0b013e3280c56ae1
41. Chang HR, Pella PM. Atazanavir urolithiasis. N Engl J Med. 2006;355(20):2158–9. http://dx.doi.org/10.1056/NEJMc061892
42. Lanzafame M, Bonora S, Lattuada E, Calcagno A, Di Perri G, Concia E. Disappearance of renal stones in an HIV-1-infected patient after reduction of atazanavir dose. AIDS Res Hum Retroviruses. 2014;30(9):835–6. http://dx.doi.org/10.1089/aid.2014.0134
43. Pacanowski J, Poirier JM, Petit I, Meynard JL, Girard PM. Atazanavir urinary stones in an HIV-infected patient. AIDS. 2006;20(16):2131. http://dx.doi.org/10.1097/01.aids.0000247571.88256.90
44. Wang LC, Osterberg EC, David SG, Rosoff JS. Recurrent nephrolithiasis associated with atazanavir use. BMJ Case Rep. 2014;2014. http://dx.doi.org/10.1136/bcr-2013-201565
45. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: Cases from the US Food and Drug Administration's Adverse Event Reporting System. AIDS. 2007;21(9):1215–8. http://dx.doi.org/10.1097/QAD.0b013e32813aee35

46. Couzigou C, Daudon M, Meynard JL, Borsa-Lebas F, Higueret D, Escaut L, Zucman D, Liotier JY, Quencez JL, Asselah K, May T, Neau D, Vittecoq D. Urolithiasis in HIV-positive patients treated with atazanavir. Clin Infect Dis. 2007;45(8):e105–8. http://dx.doi.org/10.1086/521930
47. Lafaurie M, De Sousa B, Ponscarme D, Lapidus N, Daudon M, Weiss L, Rioux C, Fourn E, Katlama C, Molina JM. Clinical features and risk factors for atazanavir (ATV)-associated urolithiasis: A case-control study. PLoS One. 2014;9(11):e112836. http://dx.doi.org/10.1371/journal.pone.0112836
48. Hamada Y, Nishijima T, Watanabe K, Komatsu H, Tsukada K, Teruya K, Gatanaga H, Kikuchi Y, Oka S. High incidence of renal stones among HIV-infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor-containing antiretroviral therapy. Clin Infect Dis. 2012;55(9):1262–9. http://dx.doi.org/10.1093/cid/cis621
49. Nishijima T, Hamada Y, Watanabe K, Komatsu H, Kinai E, Tsukada K, Teruya K, Gatanaga H, Kikuchi Y, Oka S. Ritonavir-boosted darunavir is rarely associated with nephrolithiasis compared with ritonavir-boosted atazanavir in HIV-infected patients. PLoS One. 2013;8(10):e77268. http://dx.doi.org/10.1371/journal.pone.0077268
50. Coelho S, Aparicio SR, Manso R, Soto K. Quiz page June 2012: Kidney failure in an HIV-positive patient. Am J Kidney Dis. 2012;59(6):A27–30. http://dx.doi.org/10.1053/j.ajkd.2012.03.005
51. Inagaki I, Adachi M, Ito H, Yasuda M, Tsurumi H, Deguchi T, Seishima M. Atazanavir-induced urine crystals demonstrated by infrared spectroscopic analysis. Urol Int. 2015;94(1):121–4. http://dx.doi.org/10.1159/000354735
52. Izzedine H, M'Rad M B, Bardier A, Daudon M, Salmon D. Atazanavir crystal nephropathy. AIDS. 2007;21(17):2357–8. http://dx.doi.org/10.1097/QAD.0b013e3282f17503
53. Kanzaki G, Tsuboi N, Miyazaki Y, Yokoo T, Utsunomiya Y, Hosoya T. Diffuse tubulointerstitial nephritis accompanied by renal crystal formation in an HIV-infected patient undergoing highly active antiretroviral therapy. Intern Med. 2012;51(12):1543–8. https://doi.org/10.2169/internalmedicine.51.7093
54. Viglietti D, Verine J, De Castro N, Scemla A, Daudon M, Glotz D, Pillebout E. Chronic interstitial nephritis in an HIV type-1-infected patient receiving ritonavir-boosted atazanavir. Antivir Ther. 2011;16(1):119–21. http://dx.doi.org/10.3851/imp1700
55. Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. Am J Kidney Dis. 2004;44(5):e81–4. https://doi.org/10.1053/j.ajkd.2004.07.017
56. Marinescu CI, Leyes M, Ribas MA, Penaranda M, Murillas J, Campins AA, Martin-Pena L, Barcelo B, Barcelo-Campomar C, Grases F, Frontera G, Riera Jaume M. Relationships between serum levels of atazanavir and renal toxicity or lithiasis. AIDS Res Treat. 2015;2015106954. http://dx.doi.org/10.1155/2015/106954
57. Nishijima T, Tsuchiya K, Tanaka N, Joya A, Hamada Y, Mizushima D, Aoki T, Watanabe K, Kinai E, Honda H, Yazaki H, Tanuma J, Tsukada K, Teruya K, Kikuchi Y, Oka S, Gatanaga H. Single-nucleotide polymorphisms in the UDP-glucuronosyltransferase 1a-3′ untranslated region are associated with atazanavir-induced nephrolithiasis in patients with HIV-1 infection: A pharmacogenetic study. J Antimicrob Chemother. 2014;69(12):3320–8. http://dx.doi.org/10.1093/jac/dku304
58. de Lastours V, Ferrari Rafael De Silva E, Daudon M, Porcher R, Loze B, Sauvageon H, Molina JM. High levels of atazanavir and darunavir in urine and crystalluria in asymptomatic patients. J Antimicrob Chemother. 2013;68(8):1850–6. http://dx.doi.org/10.1093/jac/dkt125
59. Cervero M, Navas E, Agud JL, Garcia-Benaya E, Mon C. Atazanavir-related renal insufficiency without concurrent tenofovir. Enferm Infecc Microbiol Clin. 2009;27(8):489–90. http://dx.doi.org/10.1016/j.eimc.2008.12.007
60. Van den Eynde E, Ferrer E, Podzamczer D. Acute renal failure and liver toxicity in an HIV/hepatitis C coinfected patient receiving telaprevir and boosted atazanavir. AIDS. 2014;28(10):1538–9. http://dx.doi.org/10.1097/qad.0000000000000265
61. Young B, Squires KE, Tashima K, Henry K, Schneider S, LaMarca A, Zhao HH, Ross LL, Shaefer MS. Estimated glomerular filtration rates through 144 weeks on therapy in HIV-1-infected subjects receiving atazanavir/ritonavir and abacavir/lamivudine or simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials. 2015;16(4):125–9. http://dx.doi.org/10.1179/1528433614z.0000000017
62. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, Gatell J, Phillips AN, Ledergerber B, Lundgren JD. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS. 2010;24(11):1667–78. http://dx.doi.org/10.1097/QAD.0b013e328339fe53
63. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, Ross M, Fux CA, Morlat P, Moranne O, Smith C, Lundgren JD. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: The D:A:D study. J Infect Dis. 2013;207(9):1359–69. http://dx.doi.org/10.1093/infdis/jit043
64. Teofilo E, Rocha-Pereira N, Kuhlmann B, Antela A, Knechten H, Santos J, Jimenez-Exposito MJ. Long-term efficacy, tolerability, and renal safety of atazanavir/ritonavir-based antiretroviral therapy in a cohort of treatment-naive patients with HIV-1 infection: The REMAIN study. HIV Clin Trials. 2016;17(1):17–28. http://dx.doi.org/10.1080/15284336.2015.1112494
65. Dbeibo L, Arif S, He F, Gupta SK. Frequency of atazanavir-associated leukocyturia development and renal function decline. AIDS. 2016;30(9):1488–9. http://dx.doi.org/10.1097/qad.0000000000001061

66. Luz AJ, Poeta J, Linden R, Antunes MV, Caminha LI, Callegari-Jacques SM, Sprinz E. Association between atazanavir plasma levels and renal function in HIV-positive individuals on antiretroviral therapy with undetectable viral load. Int J Antimicrob Agents. 2013;41(5):497–8. http://dx.doi.org/10.1016/j.ijantimicag.2013.01.013
67. Herman JS, Ives NJ, Nelson M, Gazzard BG, Easterbrook PJ. Incidence and risk factors for the development of indinavir-associated renal complications. J Antimicrob Chemother. 2001;48(3):355–60. https://doi.org/10.1093/jac/48.3.355
68. Dieleman JP, Sturkenboom MC, Jambroes M, Gyssens IC, Weverling GJ, ten Veen JH, Schrey G, Reiss P, Stricker BH. Risk factors for urological symptoms in a cohort of users of the HIV protease inhibitor indinavir sulfate: The ATHENA cohort. Arch Intern Med. 2002;162(13):1493–501. https://doi.org/10.1001/archinte.162.13.1493
69. Dieleman JP, Gyssens IC, van der Ende ME, de Marie S, Burger DM. Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. AIDS. 1999;13(4):473–8.
70. Salahuddin S, Kok DJ, Buchholz NN. Influence of body temperature on indinavir crystallization under loop of Henle conditions. J Antimicrob Chemother. 2007;59(1):114–7. http://dx.doi.org/10.1093/jac/dkl436
71. Dieleman JP, van Rossum AM, Stricker BC, Sturkenboom MC, de Groot R, Telgt D, Blok WL, Burger DM, Blijenberg BG, Zietse R, Gyssens IC. Persistent leukocyturia and loss of renal function in a prospectively monitored cohort of HIV-infected patients treated with indinavir. J Acquir Immune Defic Syndr. 2003;32(2):135–42. https://doi.org/10.1097/00126334-200302010-00004
72. van Rossum AM, Dieleman JP, Fraaij PL, Cransberg K, Hartwig NG, Burger DM, Gyssens IC, de Groot R. Persistent sterile leukocyturia is associated with impaired renal function in human immunodeficiency virus type 1-infected children treated with indinavir. Pediatrics. 2002;110(2 Pt 1):e19. https://doi.org/10.1542/peds.110.2.e19
73. Kopp JB, Miller KD, Mican JA, Feuerstein IM, Vaughan E, Baker C, Pannell LK, Falloon J. Crystalluria and urinary tract abnormalities associated with indinavir. Ann Intern Med. 1997;127(2):119–25. https://doi.org/10.7326/0003-4819-127-2-199707150-00004
74. Gagnon RF, Tecimer SN, Watters AK, Tsoukas CM. Prospective study of urinalysis abnormalities in HIV-positive individuals treated with indinavir. Am J Kidney Dis. 2000;36(3):507–15. http://dx.doi.org/10.1053/ajkd.2000.9791
75. Anglicheau D, Duvic C, Nedelec G. Sudden anuria due to indinavir crystalluria. Nephron. 2000;86(3):364–5. http://dx.doi.org/10.1159/000045803
76. Famularo G, Di Toro S, Moretti S, De Simone C. Symptomatic crystalluria associated with indinavir. Ann Pharmacother. 2000;34(12):1414–8. http://dx.doi.org/10.1345/aph.10092
77. Berns JS, Cohen RM, Silverman M, Turner J. Acute renal failure due to indinavir crystalluria and nephrolithiasis: Report of two cases. Am J Kidney Dis. 1997;30(4):558–60. https://doi.org/10.1016/S0272-6386(97)90316-4
78. Blake SP, McNicholas MM, Raptopoulos V. Nonopaque crystal deposition causing ureteric obstruction in patients with HIV undergoing indinavir therapy. AJR Am J Roentgenol. 1998;171(3):717–20. http://dx.doi.org/10.2214/ajr.171.3.9725303
79. Bruce RG, Munch LC, Hoven AD, Jerauld RS, Greenburg R, Porter WH, Rutter PW. Urolithiasis associated with the protease inhibitor indinavir. Urology. 1997;50(4):513–8. http://dx.doi.org/10.1016/s0090-4295(97)00399-3
80. Daudon M, Estepa L, Viard JP, Joly D, Jungers P. Urinary stones in HIV-1-positive patients treated with indinavir. Lancet. 1997;349(9061):1294–5. https://doi.org/10.1016/S0140-6736(05)62506-8
81. Gentle DL, Stoller ML, Jarrett TW, Ward JF, Geib KS, Wood AF. Protease inhibitor-induced urolithiasis. Urology. 1997;50(4):508–11. http://dx.doi.org/10.1016/s0090-4295(97)00401-9
82. Kalaitzis C, Dimitriadis G, Tsatidis T, Kuntz R, Touloupidis S, Kelidis G. Treatment of indinavir sulfate induced urolithiasis in HIV-positive patients. Int Urol Nephrol. 2002;34(1):13–5. https://doi.org/10.1023/A:1021340915465
83. Kohan AD, Armenakas NA, Fracchia JA. Indinavir urolithiasis: An emerging cause of renal colic in patients with Human Immunodeficiency Virus. J Urol. 1999;161(6):1765–8. https://doi.org/10.1016/S0022-5347(05)68795-2
84. Polhemus ME, Aronson NE. Persistent nephrolithiasis after discontinuation of indinavir therapy. Clin Infect Dis. 1998;27(6):1536–7. https://doi.org/10.1086/517740
85. Sundaram CP, Saltzman B. Urolithiasis associated with protease inhibitors. J Endourol. 1999;13(4):309–12. http://dx.doi.org/10.1089/end.1999.13.309
86. Witte M, Tobon A, Gruenenfelder J, Goldfarb R, Coburn M. Anuria and acute renal failure resulting from indinavir sulfate induced nephrolithiasis. J Urol. 1998;159(2):498–9. https://doi.org/10.1016/S0022-5347(01)63960-0
87. Brodie SB, Keller MJ, Ewenstein BM, Sax PE. Variation in incidence of indinavir-associated nephrolithiasis among HIV-positive patients. AIDS. 1998;12(18):2433–7. https://doi.org/10.1097/00002030-199818000-00012
88. Hermieu J, Prevot M, Ravery V, Sauty L, Moulinier F, Delmas V, Bouvet E, Boccon-Gibod L. Urolithiasis and the protease inhibitor indinavir. Eur Urol. 1999;35(3):239–41. https://doi.org/10.1159/000019854
89. Malavaud B, Dinh B, Bonnet E, Izopet J, Payen JL, Marchou B. Increased incidence of indinavir nephrolithiasis in patients with hepatitis B or C virus infection. Antivir Ther. 2000;5(1):3–5.
90. Martinez E, Leguizamon M, Mallolas J, Miro JM, Gatell JM. Influence of environmental temperature on incidence of indinavir-related nephrolithiasis. Clin Infect Dis. 1999;29(2):422–5. http://dx.doi.org/10.1086/520226

91. Meraviglia P, Angeli E, Del Sorbo F, Rombola G, Vigano P, Orlando G, Cordier L, Faggion I, Cargnel A. Risk factors for indinavir-related renal colic in HIV patients: Predictive value of indinavir dose/body mass index. AIDS. 2002;16(15):2089–93.
92. Reiter WJ, Schon-Pernerstorfer H, Dorfinger K, Hofbauer J, Marberger M. Frequency of urolithiasis in individuals seropositive for human immunodeficiency virus treated with indinavir is higher than previously assumed. J Urol. 1999;161(4):1082–4. https://doi.org/10.1016/S0022-5347(01)61595-7
93. Saltel E, Angel JB, Futter NG, Walsh WG, O'Rourke K, Mahoney JE. Increased prevalence and analysis of risk factors for indinavir nephrolithiasis. J Urol. 2000;164(6):1895–7. https://doi.org/10.1016/S0022-5347(05)66911-X
94. Ascher DP, Lucy MD. Indinavir sulfate renal toxicity in a pediatric hemophiliac with HIV infection. Ann Pharmacother. 1997;31(10):1146–9. http://dx.doi.org/10.1177/106002809703101005
95. Grabe DW, Eisele G, Miller C, Singh J, Stein D. Indinavir-induced nephropathy. Clin Nephrol. 1999;51(3):181–3.
96. Hanabusa H, Tagami H, Hataya H. Renal atrophy associated with long-term treatment with indinavir. N Engl J Med. 1999;340(5):392–3. http://dx.doi.org/10.1056/nejm199902043400515
97. Jaradat M, Phillips C, Yum MN, Cushing H, Moe S. Acute tubulointerstitial nephritis attributable to indinavir therapy. Am J Kidney Dis. 2000;35(4):E16. https://doi.org/10.1016/S0272-6386(00)70034-5
98. Marroni M, Gaburri M, Mecozzi F, Baldelli F. Acute interstitial nephritis secondary to the administration of indinavir. Ann Pharmacother. 1998;32(7–8):843–4. http://dx.doi.org/10.1345/aph.18004
99. Martinez F, Mommeja-Marin H, Estepa-Maurice L, Beaufils H, Bochet M, Daudon M, Deray G, Katlama C. Indinavir crystal deposits associated with tubulointerstitial nephropathy. Nephrol Dial Transplant. 1998;13(3):750–3. https://doi.org/10.1093/ndt/13.3.750
100. Perazella MA, Kashgarian M, Cooney E. Indinavir nephropathy in an AIDS patient with renal insufficiency and pyuria. Clin Nephrol. 1998;50(3):194–6.
101. Rajs J, Blaxhult A, Sundelin B. Sudden unexpected death as a consequence of indinavir-induced nephropathy. A case report. APMIS. 2000;108(9):581–3.
102. Reilly RF, Tray K, Perazella MA. Indinavir nephropathy revisited: A pattern of insidious renal failure with identifiable risk factors. Am J Kidney Dis. 2001;38(4):E23. https://doi.org/10.1053/ajkd.2001.27732
103. Tashima KT, Horowitz JD, Rosen S. Indinavir nephropathy. N Engl J Med. 1997;336(2):138–40. http://dx.doi.org/10.1056/nejm199701093360215
104. Cattelan AM, Trevenzoli M, Naso A, Meneghetti F, Cadrobbi P. Severe hypertension and renal atrophy associated with indinavir. Clin Infect Dis. 2000;30(3):619–21. http://dx.doi.org/10.1086/313728
105. Dieleman JP, van der Feltz M, Bangma CH, Stricker BH, van der Ende ME. Papillary necrosis associated with the HIV protease inhibitor indinavir. Infection. 2001;29(4):232–3. https://doi.org/10.1007/s15010-001-1105-y
106. Padberg J, Fritsche L, Bergmann F, Schurmann D, Suttorp N. Nephropathy and renal colic in patients treated with indinavir, ritonavir plus indinavir or ritonavir plus saquinavir. AIDS. 1999;13(15):2173–4.
107. Kopp JB, Falloon J, Filie A, Abati A, King C, Hortin GL, Mican JM, Vaughan E, Miller KD. Indinavir-associated interstitial nephritis and urothelial inflammation: Clinical and cytologic findings. Clin Infect Dis. 2002;34(8):1122–8. http://dx.doi.org/10.1086/339486
108. Grunke M, Valerius T, Manger B, Kalden JR, Harrer T. Renal dysfunction in a human immunodeficiency virus-infected patient who was treated with indinavir. Clin Infect Dis. 1997;25(5):1270–1. https://doi.org/10.1086/516978
109. Rodriguez-Hernandez MJ, Viciana P, Cordero E, de Alarcon A, Herrero M. Acute renal failure caused by indinavir in a patient with a single functioning kidney. Eur J Clin Microbiol Infect Dis. 1999;18(5):386–7.
110. Guery B, Tubiana R, Martinez F, Jacquiaud C, Bochet M, Katlama C, Deray G. Renal tolerance of indinavir in HIV-positive patients. Nephron. 1999;82(1):72. http://dx.doi.org/10.1159/000045370
111. Boubaker K, Sudre P, Bally F, Vogel G, Meuwly JY, Glauser MP, Telenti A. Changes in renal function associated with indinavir. AIDS. 1998;12(18):F249–54.
112. Rasch MG, Engsig FN, Feldt-Rasmussen B, Kirk O, Kronborg G, Pedersen C, Gerstoft J, Obel N. Renal function and incidence of chronic kidney disease in HIV patients: A Danish cohort study. Scand J Infect Dis. 2012;44(9):689–96. http://dx.doi.org/10.3109/00365548.2012.673730
113. Doco-Lecompte T, Garrec A, Thomas L, Trechot P, May T, Rabaud C. Lopinavir-ritonavir (Kaletra) and lithiasis: Seven cases. AIDS. 2004;18(4):705–6.
114. Engeler DS, John H, Rentsch KM, Ruef C, Oertle D, Suter S. Nelfinavir urinary stones. J Urol. 2002;167(3):1384–5. https://doi.org/10.1016/S0022-5347(05)65307-4
115. Benveniste O, Longuet P, Duval X, Le Moing V, Leport C, Vilde JL. Two episodes of acute renal failure, rhabdomyolysis, and severe hepatitis in an AIDS patient successively treated with ritonavir and indinavir. Clin Infect Dis. 1999;28(5):1180–1. http://dx.doi.org/10.1086/517777
116. Chugh S, Bird R, Alexander EA. Ritonavir and renal failure. N Engl J Med. 1997;336(2):138. http://dx.doi.org/10.1056/nejm199701093360214

117. Duong M, Sgro C, Grappin M, Biron F, Boibieux A. Renal failure after treatment with ritonavir. Lancet. 1996;348(9028):693. http://dx.doi.org/10.1016/s0140-6736(05)65125-2
118. Witzke O, Plentz A, Schafers RF, Reinhardt W, Heemann U, Philipp T. Side-effects of ritonavir and its combination with saquinavir with special regard to renal function. AIDS. 1997;11(6):836–8.
119. Bochet MV, Jacquiaud C, Valantin MA, Katlama C, Deray G. Renal insufficiency induced by ritonavir in HIV-infected patients. Am J Med. 1998;105(5):457. https://doi.org/10.1016/S0002-9343(98)00310-6
120. Green ST, McKendrick MW, Schmid ML, Mohsen AH, Prakasam SF. Renal calculi developing de novo in a patient taking saquinavir. Int J STD AIDS. 1998;9(9):555.
121. Lalezari JP, Henry K, O'Hearn M, Montaner JS, Piliero PJ, Trottier B, Walmsley S, Cohen C, Kuritzkes DR, Eron JJ Jr., Chung J, DeMasi R, Donatacci L, Drobnes C, Delehanty J, Salgo M. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med. 2003;348(22):2175–85. http://dx.doi.org/10.1056/NEJMoa035026
122. German P, Liu HC, Szwarcberg J, Hepner M, Andrews J, Kearney BP, Mathias A. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J Acquir Immune Defic Syndr. 2012;61(1):32–40. http://dx.doi.org/10.1097/QAI.0b013e3182645648
123. McDonald CK, Martorell C, Ramgopal M, Laplante F, Fisher M, Post FA, Liu Y, Curley J, Abram ME, Custodio J, Graham H, Rhee MS, Szwarcberg J. Cobicistat-boosted protease inhibitors in HIV-infected patients with mild to moderate renal impairment. HIV Clin Trials. 2014;15(6):269–73. http://dx.doi.org/10.1310/hct1506-269