Antiretrovirals and the kidney in current clinical practice: renal pharmacokinetics, alterations of renal function and renal toxicity

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Assessment of renal function in HIV-positive patients is of increasing importance in the context of ageing and associated comorbidities. Exposure to nephrotoxic medications is widespread, and several commonly used antiretroviral drugs have nephrotoxic potential. Moreover, specific antiretrovirals inhibit renal tubular transporters resulting in the potential for drug–drug interactions as well as increases in serum creatinine concentrations, which affect estimates of glomerular filtration rate in the absence of changes in actual glomerular filtration rate. This review explores the effects of antiretroviral therapy on the kidney and offers an understanding of mechanisms that lead to apparent and real changes in renal function.

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Introduction

The life expectancy of HIV-positive individuals exposed to combination antiretroviral therapy (cART) at the currently recommended $CD4^+$ cell count threshold approaches that of the general population [1]. As a consequence of the widespread use of cART, ageing of HIV-positive patients has been observed in many cohorts, with conditions such as cardiovascular disease, renal impairment and osteoporosis becoming more prevalent [2,3]. Chronic kidney disease (CKD), defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73 m^2 and/or proteinuria, is present in approximately 17% of HIV-positive patients [4] and is an important risk factor for cardiovascular events and death [5–8]. Older age, black ethnicity, hypertension, diabetes, low $CD4^+$ cell count, hepatitis C virus (HCV) coinfection and high HIV RNA levels have been identified as risk factors for CKD, end-stage kidney disease and renal death [9–11], and specific antiretrovirals [indinavir (IDV), tenofovir disoproxil fumarate (TDF), atazanavir (ATV) and lopinavir (LPV)] may further increase this risk [11–13].

The effects of cART on renal function have been studied in a number of settings. Initial reductions in eGFR are observed in patients who initiate cART with preserved renal function (eGFR >90 ml/min per 1.73 m^2), and

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initial increases in eGFR in those with impaired renal function, with minimal subsequent change up to 96–144 weeks [14,15]. Antiretroviral therapy may result in renal tubular dysfunction as evidenced by increased urinary concentrations of retinol-binding protein (RBP; a low-molecular-weight protein normally reabsorbed by the proximal tubule) and N-acetyl-beta-D-glucosaminidase (NAG; a proximal tubule lysosomal enzyme) [16]. Furthermore, specific antiretrovirals including IDV, TDF, ATV and LPV have been associated with acute kidney injury, CKD or CKD progression, renal impairment, renal tubular dysfunction, Fanconi syndrome or the formation of renal calculi [10–13,17–37] (Table 1). The mechanisms by which these antiretroviral drugs cause renal toxicity are complex and incompletely understood. Other drugs such as ritonavir (RTV), cobicistat (COBI), dolutegravir (DTG) and rilpivirine (RPV) inhibit drug transporters that result in reduced tubular secretion of creatinine (leading to increases in serum creatinine and reductions in eGFR) and the potential for unfavourable drug–drug interactions (Table 2) [38–42]. In this study, we review the renal pharmacokinetics including the effects on renal transporters and renal toxicity profiles of HIV drugs commonly used in or about to enter clinical practice.

Tenofovir

Following oral administration, tenofovir-DF is converted in the gut to tenofovir (TFV). Tenofovir – the renal active moiety – enters the blood stream and has a terminal elimination half-life in individuals with normal renal function of approximately 30 h [43]. Tenofovir is removed from the bloodstream by glomerular filtration and active tubular secretion. The latter is mediated through the organic anion transporters (OATs) solute carrier family (SLC) 22A6 and A8 (OAT-1 and OAT-3) on the basolateral membrane, and efflux transporters adenosine-5'-triphosphate (ATP) binding cassette (ABC)C4 and C10 [multidrug resistance protein (MRP)-4 and MRP-7] on the apical membrane [44–46] (Fig. 1). Genetic studies have reported associations between polymorphisms in ABCC4 and plasma/intracellular TFV concentrations and TFV renal clearance [44], and of polymorphisms in ABCC2 and ABCC10 with tubular dysfunction [46–48], although the role of ABCC2 in TFV transport remains uncharacterized.

Early reports linked TDF to a mild, time-dependent elevation in the serum creatinine concentration and a decrease in eGFR [49,50]. However, more recent trials of TDF [coadministered with emtricitabine (FTC) and efavirenz (EFV)] have shown no effect on serum creatinine and eGFR out to 96 weeks in cART-naive patients [22,51–53], and no effect on eGFR at 48 weeks in patients who switched from zidovudine/lamivudine (ZDV/3TC) to TDF/FTC [54]. By contrast, a number of clinical trials have shown initial reductions in eGFR of 10–15% in patients in whom TDF is initiated with RTV or COBI-boosted protease inhibitors or integrase inhibitors (INIs); seemingly, a new steady state is reached after 4 weeks, with no further decline up to 2 years [see COBI/elvitegravir (EVG) below] [22,23]. In cohort studies, greater reductions in eGFR have been observed when TDF was coadministered with RTV-boosted protease inhibitor vs. NNRTI [55,56]. The observed reductions in eGFR may relate to the 30% increase in plasma TFV concentrations when TDF is coadministered with RTV [57]. The combined effects of increased tubular TFV exposure, of RTV or COBI on tubular TFV excretion and/or of RTV or COBI on eGFR by inhibiting the tubular creatinine transporter multidrug and toxin extrusion 1 (MATE1) without affecting the

Table 1. Current antiretrovirals and their effects on the kidney.

Antiretroviral drug(s)	Alteration of renal function [(generally) not treatment-limiting]	Treatment-limiting renal disease
Tenofovir disoproxil fumarate	Renal tubular dysfunction [18]; eGFR decline >3 ml/min per 1.73 m^2 per year [13]; Proteinuria (nonglomerular origin) [13,27]; Chronic kidney disease [11,13]	Acute kidney injury (rare)[a] [28]; Tubulo-interstitial nephritis (rare)[a] [30]; Renal tubular disease/ Fanconi syndrome (uncommon) [19,25]; CKD with progressive eGFR decline [17]
Ritonavir/atazanavir	Inhibition of tubular creatinine secretion [23,36]; Renal tubular dysfunction [24,37]; Crytalluria [33]; eGFR decline >3 ml/min per 1.73 m^2 per year [13]; Chronic kidney disease [11]	Acute kidney injury (rare)[a] [30]; Tubulo-interstitial nephritis (rare)[a] [30]; Nephrolithiasis (uncommon) [20,21]
Ritonavir/lopinavir	Chronic kidney disease [11,12]	Nephrolithiasis (rare)[a] [32]
Cobicistat/elvitegravir (along with tenofovir-DF/emtricitabine)	Inhibition of tubular creatinine secretion [22,23]	AKI (uncommon)[a] [22,23]; Renal tubular disease/ Fanconi syndrome (uncommon) [22]
Cobicistat/atazanavir (along with tenofovir-DF/emtricitabine)	Inhibition of tubular creatinine secretion [36]	AKI (uncommon)[a] [36]; Renal tubular disease/ Fanconi syndrome (uncommon) [36]
Dolutegravir	Inhibition of tubular creatinine secretion [34]	None reported
Rilpivirine	Inhibition of tubular creatinine secretion [35]	None reported
Raltegravir	Inhibition of tubular creatinine secretion? [34]	None reported
Ritonavir/darunavir	Crystalluria [33]	Nephrolithiasis (rare)[a] [32]

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Limited evidence (case series or case reports only).

Table 2. Renal tubular transporters that are inhibited by or for which antiretrovirals are substrate [38–42].

Transporter	Selected inhibitors	Selected substrates	Resulting drug–drug interaction
Basolateral membrane			
OAT1 (SLC22A6)	Probenecid, NSAIDs, furosemide, mycophenolate, olmesartan, ritonavir	Cidofovir, adefovir, furosemide, ciprofloxacin, methotrexate, captopril, dolutegravir, lamivudine, tenofovir, didanosine	Acyclovir and didanosine increase serum concentrations of tenofovir; Tenofovir increases didanosine levels; Probenecid may decrease the incidence of renal tubular toxicity by tenofovir.
OAT3 (SLC22A8)	Probenecid, salicylate, NSAIDs, gemfobrozil, mycophenolate, ritonavir	NSAIDS, methotrexate, pravastatin, furosemide, benzylpenicillin, tenofovir	
OCT2 (SLC22A2)	Cimetidine, cetirizine, quinine, testosterone, clonidine, procainamide, carvedilol, bisoprolol, ranitidine, dolutegravir, rilpivirine	Amantadine, metformin, cisplatin, cimetidine, quinine, pindolol, metotrexate, ranitidine, lamivudine, creatinine	Increased serum creatinine concentration (translating into reductions in creatinine clearance and eGFR) with dolutegravir and rilpivirine
Apical membrane			
P-glycoprotein 1 (ABCB1)	Clarithromycin, quinidine, itraconazole, verapamil, cyclosporin A, ritonavir, cobicistat	Digoxin, daunorubicin, vinblastin, doxorubicin, paclitaxel, docetaxel, quinidine, verapamil, saquinavir, ritonavir	
MRP1 (ABCC1)	Probenecid, efavirenz	Daunorubicin, etoposide, methotrexate, vincristine	
MRP2 (ABCC2)	Probenecid, efavirenz, ritonavir	Daunorubicin, etoposide, methotrexate, vincristine, cisplatin, methotrexate, lopinavir, tenofovir (?)	NB: Effect of RTV on TFV efflux suspected but not confirmed *in vitro*
MRP4 (ABCC4)	Probenecid, dipyridamole, NSAIDs, cidofovir, acyclovir, gancyclovir, ritonavir	Adefovir, zidovudine, prostaglandins, methotrexate, tenofovir	Acyclovir increases serum concentrations of tenofovir; NSAIDs may enhance tenofovir nephrotoxicity
MRP7 (ABCC10)	Sildenafil, vardenafil	Tamoxifen, docetaxel, paclitaxel, daunorubicin, vincristine, etoposide, tenofovir, nevirapine	
MATE1 (SLC47A1)	Metformin, quinidine, rapamycin, cimetidine, trimethoprim, pyrimethamine, ritonavir, cobicistat	Cephalexin, cimetidine, procainamide, metformin, oxaliplatin, creatinine, lamivudine	Increased serum creatinine concentration (reductions in creatinine clearance and eGFR) with ritonavir and cobicistat

eGFR, estimated glomerular filtration rate; OCT, organic cation transporter; RTV, ritonavir; TFV, tenofovir.

actual GFR [58] may contribute to these greater eGFR reductions. Of note, bioequivalence studies with COBI showed no increase in TFV exposure (although FTC concentrations increased slightly) [59], and the effects of TDF/FTC along with a boosted protease inhibitor (ATV/RTV) on eGFR were not observed with abacavir (ABC)/3TC in the ACTG5202 study [60].

Subclinical renal tubular dysfunction, characterized by reduced phosphate reabsorption and increased urinary concentrations of glucose and/or low molecular weight proteins, has been reported with TDF in 9–81% of patients [16,18,24,61]. Studies have shown an increase in urinary RBP or alpha1 microglobulin concentration following TDF initiation [51,54]. Risk factors for TDF-associated renal tubular dysfunction include older age, low BMI, underlying CKD and the presence of genetic polymorphisms in the genes encoding MRP2, MRP4 and MRP7 [46–48]. The clinical significance of renal tubular dysfunction is poorly understood, both in terms of renal disease progression and bone loss.

The most serious complication of TDF is Fanconi syndrome, an acquired form of severe renal tubular disease [19,25,62]. Fanconi syndrome is characterized by profound hypophosphataemia and normoglycaemic glycosuria and has been observed in 0.5–1% of patients in clinical trials [26,36,52] and 1–1.5% of patients in cohort studies [19]. Urinary concentration defects are common, and osteomalacia resulting from phosphate wasting may give rise to bone pain and pathological fractures [19,63]. Tenofovir-DF has also been associated with incident CKD [11,13,64], proteinuria [13,27], renal impairment [12] and rapid or accelerated eGFR decline [13,17]. The higher incidence of these renal adverse events in observational cohort studies may be explained by the exclusion in clinical trials of patients at greatest risk of these events. Although acute kidney injury (AKI) has been described in patients receiving TDF [28,65], a large observational cohort study [66] found no evidence for an increased incidence of AKI following TDF exposure.

The cause of TFV-associated eGFR reductions remains unclear. Tenofovir has minimal effect on GFR as measured by iothalamate clearance [54]. It is possible that a direct toxic effect on tubular mitochondria affects renal tubular creatinine secretion, as this is an energy-dependent process [67]. Alternatively, TFV

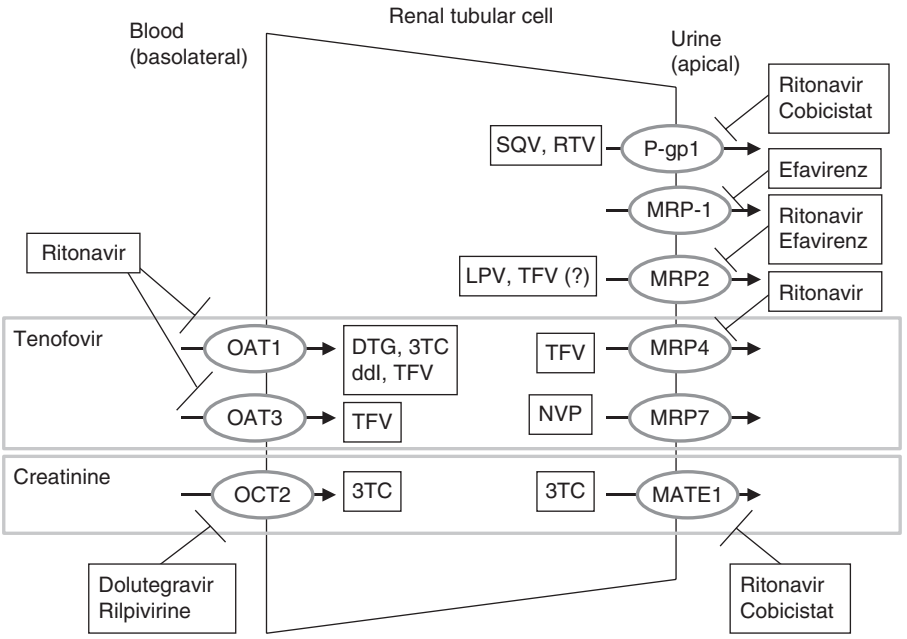

Fig. 1. Effect of antiretrovirals on renal tubular transporters. Multiple transporters on the basolateral and apical membranes are subject to the inhibitory effects of antiretrovirals; the former may result in reduced uptake of drugs and other compounds from the blood stream giving rise to increased plasma concentrations, while the latter may give rise to reduced excretion of drugs and other compounds into the urinary space leading to increased intratubular concentrations and potential tubular toxicity. Tubular secretion of creatinine is affected by the inhibitory effects of dolutegravir and rilpivirine on OCT2 and the inhibitory effects of ritonavir and cobicistat on MATE1. Increased tubular toxicity with tenofovir has been associated with polymorphisms in MRP2 and MRP4 and has been linked to the inhibitory effects of ritonavir on these apical membrane transporters. 3TC, lamivudine; ddI, didanosine; DTG, dolutegravir; LPV, lopinavir; MATE, multidrug and toxin extrusion; MRP, multidrug resistance protein; NVP, nevirapine; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; SQV, saquinavir; TFV, tenofovir.

may directly affect the tubular transporters implicated in creatinine secretion, although this is not corroborated by in-vitro data (Fig. 1) [68]. In patients with frank nephrotoxicity, renal biopsies have revealed acute tubular necrosis with distinctive proximal tubular eosinophilic inclusions representing giant mitochondria on light microscopy. Electron microscopy showed mitochondrial enlargement, depletion and dysmorphic changes [28]. In the majority of patients, eGFR decline improves and renal tubular dysfunction appears – at least partially – reversible upon TDF discontinuation, although this is largely based on reversibility of serum creatinine elevations and data on restoration of renal tubular function remain sparse [19,28,69].

Of interest is a new formulation of TFV, TFV alafenamide fumarate (TAF), which is currently being investigated in phase 3 clinical trials. This prodrug leads to higher intracellular TFV-diphosphate concentrations with much reduced systemic TFV exposure. Moreover, its neutral charge suggests that it is not a substrate for renal OAT [70]. Preliminary data show that TAF, compared with TDF, results in smaller reductions in eGFR, a somewhat reduced incidence of proteinuria and hypophosphataemia, and smaller reductions in bone mineral density when coadministered with COBI, EVG and FTC [71].

Ritonavir/atazanavir

Ritonavir, a protease inhibitor, was first developed as an active antiretroviral drug. However, dose-related adverse events limited its use as an active agent in cART. Current use of RTV is for its potent inhibition of cytochrome P4503A4 (CYP3A4), the primary enzyme involved in the metabolism of many drugs including protease inhibitors, and inhibition of the permeability glycoprotein 1 (P-gp), a cell membrane efflux transporter of various substrates including protease inhibitors. Together, these effects result in 'boosted' plasma concentrations of concomitantly administered protease inhibitors (and other drugs). Ritonavir is approximately 99% bound to plasma proteins, including albumin and alpha1-acid glycoprotein [72]. About 34 and 3.5% of a 600 mg dose is excreted as unchanged drug in the faeces and urine, respectively.

In renal tubular cells, RTV inhibits several transporters including OAT1, OAT3, MRP2, MRP4 and MATE1 (Table 2). Data from in-vitro experiments suggest that RTV has a minimal effect on MRP4, the apical tubular TFV transporter [73]. However, increased tubular TFV exposure may result from the inhibitory effect of RTV on P-gp [74], genetic studies have linked polymorphisms in MRP2 with tubulopathy [26,27] and clinical studies

have linked severe tubulopathy to RTV coadministration [19,25].

Atazanavir is rapidly absorbed and 86% protein bound in the circulation. As for other protease inhibitors, ATV is extensively metabolised by CYP3A isoenzymes. When coadministered with RTV 100 mg, ATV $AUC_{0-24\,h}$ and C_{min} were increased by three to four-fold and approximately 10-fold, respectively, compared with ATV 300 mg alone [75]. Up to 8% of ATV is excreted unchanged in the kidney via glomerular filtration; the drug is poorly soluble in urine and especially likely to precipitate at alkaline pH [76].

Early reductions in creatinine clearance and eGFR, with stable measurements thereafter, have been reported in several clinical trials of ATV/RTV (along with TDF/FTC) including the Gilead 0103 and 0114 studies [23,26,36], the BASIC study [77] and an Italian pilot study [78]. In the CASTLE study, patients on ATV/RTV (plus TDF/FTC) experienced little change from baseline to week 48 in creatinine clearance (median −1%), and no patients discontinued ATV/RTV for renal adverse events [79]. These initial changes in eGFR/creatinine clearance are consistent with the inhibitory effect of RTV on tubular creatinine secretion via MATE1 (Fig. 1). However, in the ACTG 5202 trial, ATV/RTV coexposure with TDF/FTC, but not ABC/3TC, resulted in reductions in creatinine clearance (−3.1 vs. +3.3 ml/min at 48 weeks, −3.1 vs. +5.2 ml/min at 96 weeks) [60], which may reflect the effect of RTV on systemic TFV exposure or an interaction between RTV (or ATV) and TFV at the level of the renal tubule. ATV/RTV has also been associated with CKD progression [11,64] and eGFR decline [12,37] in observational cohort studies, although others have found that reductions in eGFR with ATV/RTV (along with TDF/FTC) were largely restricted to the first 6 months [80], and with subclinical renal tubular dysfunction [24,37].

Renal tubular disease/Fanconi syndrome has been reported in patients who received ATV/RTV with TDF/FTC. In the Gilead 0103/0114 studies, 0.6–1.4% of patients in the ATV/RTV arms discontinued study drug owing to renal events including two individuals who had proximal tubulopathy [23,36]. In addition, several studies have reported crystalluria and nephrolithiasis with ATV/RTV [29], with an incidence of 7.3–23.7 per 1000 person-years [20,21]. In several case reports, stones have been retrieved that consisted of pure ATV, while others reported an associated chronic interstitial nephritis on kidney biopsy [30,81]. The risk factors for stone formation remain to be fully elucidated; one study [20] suggested that CKD (eGFR <60 ml/min per 1.73 m^2) may be a risk factor for ATV-associated nephrolithiasis.

Ritonavir/lopinavir

The rapid and extensive first-pass oxidative metabolism of LPV in the liver is mediated primarily by CYP3A4/5 isoenzymes; RTV inhibits the activity of CYP3A4 in a concentration-dependent manner in human liver microsomes resulting in increased plasma lopinavir concentrations [31]. In-vitro studies have also implicated MRP2 in active cellular efflux of LPV, with specific single nucleotide polymorphisms (4544G>A) resulting in reduced ATPase activity and LPV accumulation in stably transfected human embryonic kidney cells [82]. Lopinavir/ritonavir has been shown to reduce TFV renal clearance by 17.5% [38], although this may reflect the effects of RTV rather than that of LPV.

In the ARTEMIS study, similar modest decreases in creatinine clearance were observed in both arms (−9.3 vs. −7.0 ml/min for darunavir (DRV)/RTV and LPV/RTV along with TDF/FTC respectively, and six patients in each arm developed kidney stones [32]. In the CASTLE study, patients receiving LPV/RTV (along with TDF/FTC) experienced little change from baseline to week 48 in creatinine clearance (median −1%), and no patients discontinued for renal adverse events [79]. Young *et al.* [80] reported small (−2.6 ml/min per 1.73 m^2) initial eGFR reductions with LPV/RTV (along with TDF/FTC). Some observational cohort studies reported LPV/RTV to be associated with incident CKD or the development of renal impairment, although the incidence rate ratios were relatively small (1.08–1.22 per year of exposure) [11,12], whereas others found no association between LPV/RTV and incident CKD, proteinuria, rapid eGFR decline or proximal renal tubular dysfunction [13,37]. It remains unclear whether LPV/RTV has intrinsic nephrotoxic properties, or whether LPV/RTV merely enhances the nephrotoxic potential of coadministered drugs, especially TDF.

Ritonavir/darunavir

Darunavir is a nonpeptidic peptidomimetic protease inhibitor. The oral bioavailability of a single 600 mg dose of DRV along with 100 mg RTV is 82%. Darunavir/ritonavir is an inhibitor of P-gp and, when administered with food, DRV C_{max} and AUC are approximately 40% higher relative to the fasting state. Darunavir is approximately 95% bound to plasma proteins, mainly alpha 1-acid glycoprotein (AAG), and is extensively metabolized by CYP3A. Approximately 79.5% of the administered dose of DRV is recovered in the faeces as either inactive metabolite or unchanged drug (approximately 40%) [83]. The terminal elimination half-life of DRV was shown to be 6.5 h, which was lower than the 0 to 24-h half-life of 10.7 h [84].

Darunavir was not included in the analyses that examined the relationship between individual antiretrovirals and CKD, rapid eGFR decline or proteinuria [11,13]. The early changes in eGFR observed with RTV as described above for ATV and LPV have also been observed with DRV [32]. In a recent study, ATV and DRV crystals were found in 8.9 and 7.8% of patients,

respectively [33], and in the ARTEMIS study, six patients each in the DRV and LPV arms developed kidney stones [32].

Cobicistat/elvitegravir

Cobicistat is a potent inhibitor of CYP3A and has no antiviral activity against HIV. Although COBI and RTV have similar inhibitory effects on CYP3A4, CYP2B6 and P-gp, COBI is a weak inhibitor of CYP2D6, does not inhibit CYP1A2, CYP2C9 or CYP2C19, and has a low propensity for activating xenobiotic receptors such as the aryl hydrocarbon, pregnane X and the constitutive androstane receptor [42,85–88]. Cobicistat is extensively metabolized through CYP3A, and following glucuronidation, it is primarily eliminated via the faeces; urinary excretion is low ($8.2 \pm 1.1\%$).

Elvitegravir is a novel INI that is metabolized by CYP3A enzymes and predominantly eliminated via the faeces following glucuronidation; 6.7% of the administered dose is recovered in urine [89,90]. Cobicistat at a dose of 150 mg once daily increases EVG exposure approximately 20-fold and to a similar extent as RTV 100 mg, thereby allowing once-daily dosing [59,91,92]. COBI was also shown to be a suitable booster for ATV and DRV, but not tipranavir [93–95]. Neither COBI nor EVG require dose modification in patients with severe renal impairment (creatinine clearance <30 ml/min) [58] or moderately advanced liver disease (Child-Pugh-Turcotte class B) [96].

Similar to RTV, cimetidine and trimethoprim, COBI is an inhibitor of MATE1 that mediates tubular secretion of creatinine (Fig. 1) [38]. Abrogation of tubular creatinine secretion results in moderate increases in serum creatinine concentration and moderate reductions in creatinine clearance (by Cockcroft–Gault) or eGFR. In healthy volunteers, COBI exposure resulted in reduced creatinine clearance with minimal change in the actual (iohexol-measured) glomerular filtration rate (−9.9 vs. −2.7 ml/min in those with creatinine clearance >80 ml/min, and −11.9 vs. −3.6 ml/min in those with creatinine clearance 50–79 ml/min). The changes in creatinine clearance were reversible upon drug discontinuation; baseline creatinine clearance (range 50–140 ml/min) did not affect the magnitude of the reduction in creatinine clearance with COBI exposure [58]. Administration of COBI/EVG, together with TDF/FTC, in the phase 3 trial programme increased serum creatinine levels by 10–15% and reduced creatinine clearance by approximately 10% (10–15 ml/min) [26,52]. These changes were observed within 4 weeks of treatment initiation at which time a new 'set point' was reached with minimal subsequent change up to week 96 (−2.6 vs. −1.0 ml/min in the 0102 study, −1.8 vs. −4.4 ml/min in the 0103 study) [22,23,26,52].

In these phase 3 trials, five patients (1.4%) exposed to COBI/EVG/TDF/FTC in the 0102 study experienced renal events (elevated serum creatinine in two, renal failure in two, Fanconi syndrome in one); a total of four patients had evidence of proximal tubulopathy that led to study drug discontinuation before week 48 [52]. A further two patients (0.6%) discontinued study drug between weeks 48 and 96 because of renal adverse events consisting of serum creatinine elevations not accompanied by proximal tubulopathy [22]. In the 0103 study, three patients (0.8%) discontinued study drug due to renal events out to week 96 [23]. In the pooled dataset, the incidence of proteinuria was somewhat higher with COBI/EVG (5.9%) and RTV/ATV (4.3%) than with EFV/TDF/FTC (1.9%) [97].

Although inhibition of MATE1 by COBI should not affect elimination of TFV, which is a substrate of OAT1/3 and MRP4 [68], the occurrence of several cases of renal tubular disease in low-risk individuals exposed to COBI/TDF in the phase 3 programme may point towards an interaction between these two drugs at the level of the tubular transporters. A similar interaction has previously been proposed for RTV [4] and is supported by a trend towards lesser change in eGFR and other renal biomarkers with TAF/COBI vs. TDF/COBI [71].

Cobicistat/atazanavir

In the Gilead 0114 study, 692 patients with creatinine clearance more than 70 ml/min were randomized 1 : 1 to receive COBI or RTV, each with ATV/TDF/FTC. Patients in the COBI arm experienced greater reductions in creatinine clearance (−13 vs. −9 ml/min) than those in the RTV arm; 1.7 vs. 1.4% of patients discontinued study medication for renal events, and five vs. two patients had proximal tubulopathy [36].

Cobicistat/darunavir

The clinical utility of COBI-boosted DRV is being explored in a phase II clinical trial comparing COBI/DRV along with TDF/FTC vs. COBI/DRV/TDF/FTC as a single tablet formulation (NCT01565850). COBI/DRV was recently licensed for the treatment of HIV-positive patients in Canada.

Dolutegravir

Dolutegravir is a novel INI with low pharmacokinetic variability and concentration–time profiles supporting once-daily administration [98,99]. Dolutegravir is primarily metabolized by glucuronidation and excreted via the faeces, with minimal amounts excreted in urine (<1%). Dolutegravir is an inhibitor of organic cation transporter 2 (OCT2) [100]; other drugs that are substrate for this transporter include metformin, pindolol, procainamide, ranitidine and varenicline. Consequently, DTG may adversely interact with OCT2 substrates with a narrow therapeutic range such as dofetilide, which is used to treat cardiac arrhythmias [101].

The basolateral membrane transporter OCT2 also mediates tubular uptake of creatinine (Fig. 1). Consequently, DTG exposure results in increases in serum creatinine and moderate reductions (10–15%) in eGFR without changes in actual (iohexol-measured) GFR [102]. In clinical trials, DTG was associated with moderate reductions in creatinine clearance (mean −16.5 ml/min); no grade 3–4 elevations of serum creatinine were observed, and no patients discontinued DTG for renal toxicity [103]. The combined 48-week results from the DTG SPRING-2 and SINGLE studies showed reductions in creatinine clearance with both raltegravir (RTG) and DTG (−5.4 vs. −16.5 ml/min), suggesting that renal tubular effects with INI may be more common than previously realized [34].

Raltegravir

Raltegravir is absorbed with a T_{max} of approximately 3 h postdose in the fasted state and has shown considerable interindividuals and intraindividual pharmacokinetic variability. Raltegravir is approximately 83% bound to plasma proteins. The major mechanism of clearance of raltegravir is uridine diphosphate glucuronyltransferase (UGT)1A1-mediated glucuronidation (responsible for the formation of the inactive metabolite raltegravir-glucuronide) with no involvement of CYP450. The apparent terminal half-life of raltegravir is approximately 9 h, and approximately 51 and 32% of the dose are excreted in faeces and urine, respectively [104]. Its lack of effect on CYP450 renders RTG relatively free of drug–drug interactions [89].

Raltegravir was not included in the analyses that examined the relationship between individual antiretrovirals and CKD, rapid eGFR decline or proteinuria [11,13]. The early changes in creatinine clearance observed with DTG have also been seen with RTG albeit to a lesser extent. Although the time-dependent pattern is consistent with an inhibitory effect of RTG on tubular creatinine transport, the mechanism has not been reported. Several cases of rhabdomyolysis, including one patient with AKI secondary to rhabdomyolysis [105], have been reported with RTG.

Rilpivirine

Rilpivirine has been shown to be an inhibitor of P-gp, breast cancer resistance protein (BCRP), OCT2, OATP1B1, CYP3A4, CYP2C19 and CYP2B6. It is not a substrate of P-gp, BCRP, or MRP 1 and 2 [106]. Furthermore, in-vitro studies showed that RPV induced mRNA expression of ABCB1, CYP3A4 and UGT1A3, whereas ABCC1, ABCC2, ABCG2, OATP1B1 and UGT1A9 were not induced. Moreover, RPV was a PXR activator. Although RPV inhibits and induces several relevant drug-metabolizing enzymes and drug transporters, it has a relatively low potential for drug–drug interactions because of its low plasma concentration.

As a weak inhibitor of OCT2, exposure to RPV results in a small increase of serum creatinine; this increase was independent of the RPV dose and translates into moderate (5–11 ml/min per 1.73 m^2) reductions in eGFR [53,107]. There were no grade 3–4 creatinine abnormalities, and no patients discontinued RPV for renal adverse events [108].

Antiretrovirals and the kidney: opinion-based recommendations for clinical practice

Many of the current and forthcoming antiretrovirals have the potential to affect kidney function. Rilpivirine, DTG, COBI, RTV, and possibly RTG, affect tubular creatinine transport without apparent renal toxicity. Lopinavir/ritonavir has been associated with eGFR decline, although evidence for direct adverse effects on the kidney is currently lacking. Tenofovir-DF and ATV clearly have nephrotoxic potential, although overt renal toxicity is uncommon. The challenge in clinical practice is to distinguish the benign mild to moderate aberrations in renal biomarkers from clinically significant toxicity.

International guidelines, based on expert opinion, recommend that renal function (eGFR and urinalysis) is assessed at the time of HIV diagnosis, prior to initiating cART, and during clinical follow up [109–111]. It seems prudent to adhere to this recommendation and ensure that renal function is reassessed after 4 weeks in those who receive RPV, DTG, COBI, RTV and RTG to establish the new 'eGFR setpoint' as a reference to compare subsequent measurements. eGFR declines of 10–20% can be anticipated with these drugs and should not immediately raise concern if nonprogressive and seen in isolation. Patients with substantial eGFR reduction at 4 weeks should have this rechecked a month later to ensure that no further decline has occurred. Where these drugs are coadministered with TDF, urinalysis and measurement of urine protein: creatinine ratio should be performed to rule out (worsening) proteinuria, haematuria or normoglycaemic glycosuria as manifestations of renal tubular disease. Tubular function can be further evaluated by measurement of low molecular weight proteins and calculation of the fractional excretion of phosphorus if (fasting) hypophosphataemia is present [112]. In most patients stable on cART with undetectable HIV RNA levels and preserved renal function, annual assessment of renal function is likely to suffice, although the optimal frequency of renal monitoring has not been studied.

In patients with normal renal function, progression to advanced CKD (eGFR <30 ml/min per 1.73 m^2) is very uncommon [8,10] and drugs such as TDF and ATV

Table 3. Changes in creatinine clearance in tenofovir disoproxil fumarate/emtricitabine-treated patients with commonly used antiretrovirals.

	Antiretroviral drug(s)	Change in creatinine clearance (ml/min) up to 192 weeks	Reference
Minimal or no change	Efavirenz	−0.8	[22,53]
Moderate decrease	Rilpivirine[a]	−5 to −11	[53,107]
	Raltegravir	−5.4	[34]
	Ritonavir/lopinavir	−7.0	[32]
	Ritonavir/atazanavir	−9.1 to −9.5	[23,36]
	Ritonavir/darunavir	−9.3	[32]
Greatest decrease	Cobicistat/elvitegravir	−12.7 to −14.3	[22,23]
	Cobicistat/atazanavir	−12.9	[36]
	Dolutegravir[a]	−16.5	[34]

[a]Includes patients on abacavir/lamivudine and/or zidovudine/lamivudine.

have an excellent safety profile in these individuals. By contrast, patients with impaired renal function are at a greater risk of renal disease progression and should be monitored more carefully. The risk of eGFR decline and overt renal toxicity is increased with TDF and ATV/RTV [11,13,17,20,64], and these drugs are best avoided in patients with CKD and impaired renal function [113].

Substantial fluctuations between serum creatinine measurements are observed in clinical practice, and treatment decisions should not be based on single GFR estimates [112]. Previous eGFR measurements, urinalysis, clinical status, comorbidities and comedications are important in establishing the probable cause of renal dysfunction. Rapidly progressive decline in eGFR and significant proteinuria (>500−1000 mg/24 h) are distinctly uncommon and should lead to further investigations to establish the exact cause. This includes a renal ultrasound and not infrequently a renal biopsy. Conversely, more gradual eGFR decline and/or mild–moderate proteinuria should focus on a review and management of risk factors, including hypertension, diabetes mellitus, exposure to nephrotoxic medications and urological disease, and liaison with a nephrologist should be considered [17].

Conclusion

Rilpivirine, DTG, COBI and RTV, although not intrinsically nephrotoxic, affect the clinically useful relationship between serum creatinine and eGFR (Table 3) [22,23]. Renal function should be reassessed approximately 4 weeks after initiation of these drugs to evaluate the new eGFR set point. Renal tubular disease requiring TDF discontinuation occurred in 0.5% of clinical trial participants who received TDF together with COBI or RTV, indicating that clinicians should remain vigilant of this complication. Tenofovir-DF and ATV are best avoided in patients with CKD, and preliminary data suggest that TAF, a new formulation of TFV, may have an improved renal safety profile. Several of these drugs are being made available as single tablet regimens that facilitate convenient once-daily dosing in patients with normal kidney function. However, the fixed-dose TDF in these combination tablets renders them less suitable for patients with acute severe illness in whom AKI is relatively common and in whom full-dose TDF may cause further kidney injury.

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Conflicts of interest

J.C.Y. has received funding to attend conferences or educational meetings, honoraria and travel bursaries from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Abbvie. A.P. has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Merck. M.B. has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Merck. R.J. has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Abbvie. S.K. has received funding for research, travel bursaries, speaker's honoraria and support for a drugs interactions website from Gilead, Janssen, ViiV, Bristol Myers Squibb, Boehringer and Merck. J.L. has received funding to attend educational meetings and honoraria from Gilead Sciences and ViiV Healthcare. F.A.P. has received funding to attend conferences or educational meetings, honoraria and/or funding for research from Abbvie, Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag, GlaxoSmithKline/ ViiV Healthcare and Merck.

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