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REVIEW

HIV, drugs and the kidney

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Abstract

Human immunodeficiency virus (HIV) affects over 36 million people worldwide. Antiretroviral therapy (ART) is expanding and improving HIV viral suppression, resulting in increasing exposure to drugs and drug interactions. Polypharmacy is a common complication as people are living longer on ART, increasing the risk of drug toxicities. Polypharmacy is related not only to ART exposure and medication for opportunistic infections, but also to treatment of chronic lifestyle diseases. Acute kidney injury (AKI) is frequent in HIV and is commonly the result of sepsis, dehydration and drug toxicities. Furthermore, HIV itself increases the risk of chronic kidney disease (CKD). Drug treatment is often complicated in people living with HIV because of a greater incidence of AKI and/or CKD compared to the HIV-negative population. Impaired renal function affects drug interactions, drug toxicities and importantly drug dosing, requiring dose adjustment. This review discusses ART and its nephrotoxic effects, including drug–drug interactions. It aims to guide the clinician on dose adjustment in the setting of renal impairment and dialysis, for the commonly used drugs in patients with HIV.

Keywords: drugs interactions, HIV, kidney injury, nephrotoxicity, renal dose adjustment.

Citation

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Introduction

In 2018, 37.9 million people worldwide were living with human immunodeficiency virus (HIV), and there were 1.7 million new infections reported.[1] Africa is still the most affected region, where 27.5 million people are HIV positive; this includes two-thirds of the new infections.[1] South Africa (SA) continues to have the highest HIV burden worldwide, with an estimated 7.52 million documented to be HIV positive in 2018 (12.4% of the population).[2]

Therapeutics in HIV is often complicated by the increased incidence of acute kidney injury (AKI) and/or chronic kidney disease (CKD). Drug toxicity itself remains a leading cause for AKI in this population.[3–7] Furthermore, given the high prevalence of renal dysfunction in HIV, dosing and prescription of medication need to be carefully considered. This is particularly important as people living with HIV (PLWH) have a 2- to 20-fold greater risk of end stage renal disease (ESRD) compared with the general population.[8–11] The reported prevalence of HIV-associated CKD ranges from 4.7 to 38% globally. The wide variation is due to differing definitions used to determine CKD, access to healthcare and genetic predisposing risk.[12]

Compounding the complexity of prescribing in HIV is the frequent need for polypharmacy due to co-infections with opportunistic infections, for example, *Mycobacterium tuberculosis* (MTB). The World Health Organisation (WHO) reports MTB as a global health emergency.[13] For the past 5 years, it has been ranking above HIV as the leading cause of death from a single infectious agent.[14] Three-quarters of the HIV-associated MTB cases occur in Africa.[13] Drug metabolism and the pharmacokinetics of antiretroviral therapy (ART) are often affected by coadministration with MTB drugs (e.g. lopinavir with rifampicin). In addition, MTB can also affect the kidney directly in a number of ways, including granulomatous interstitial nephritis (GIN)[15] and genitourinary MTB leading to obstructive uropathy.[16]

This review serves to, firstly, evaluate potential nephrotoxicities and drug interactions of commonly used medications in the setting of HIV. Secondly, it aims to guide the clinician in drug choice and dosing alterations required in the setting of

renal impairment in HIV. It will also include how to manage drug dosing in the setting of dialysis and transplantation. In order to address the challenges of medication use in PLWH and kidney disease, this review is divided into three sections: ART, polypharmacy and prescribing in renal impairment. Information was gathered from literature that provided a practical guidance on how to manage drug use in PLWH with renal dysfunction.

Antiretrovirals and their effects on the kidney

Nucleotide reverse transcriptase inhibitors

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NRTI) and is currently recommended by the WHO as a first-line agent for the treatment of HIV infection. TDF is eliminated by the kidneys through glomerular filtration and active proximal renal tubular secretion. It enters proximal tubular cells through organic anion transporters 1 and 3 and is primarily secreted into the tubular lumen through multidrug resistance proteins 2 and 4.[17] TDF has once-daily dosing and is generally safe and well tolerated, but it has important potential for cumulative nephrotoxicity.

Subclinical proximal tubular dysfunction (low-level proteinuria and excessive phosphaturia) is common. Approximately 1–2% of TDF recipients develop treatment-limiting tubulopathy, which may manifest as Fanconi syndrome. Risk factors for tubulopathy include age, immunodeficiency, diabetes, prolonged exposure and concomitant use of didanosine or ritonavir-boosted protease inhibitors (PIs).[18] Numerous drugs interfere with the cotransporters responsible for drug excretion in the proximal tubule. TDF nephrotoxicity may be enhanced by the co-administration of acyclovir, cidofovir, valacyclovir, ganciclovir, valganciclovir, dipyridamole, non-steroidal anti-inflammatory drugs, probenecid and ritonavir.[19]

Severe tubulopathy may cause a decline in estimated glomerular filtration rate (eGFR), osteomalacia and pathological fractures. Mocroft et al.[20] investigated 23,905 PLWH to assess the association between duration of exposure to TDF and the development of CKD in people with normal renal function at ART initiation. During a median follow-up period of 7.2 years, 285 (1%) developed CKD. There was also a significant increase in CKD associated exposure to TDF, with a 1.94-fold increased incidence risk at 5 years, when compared to baseline. This was not detected with cumulative exposure to abacavir. This suggests a cumulative toxic effect of tenofovir. Wever and colleagues observed stabilisation or improvement in eGFR in individuals who discontinued TDF with an eGFR of <60 mL/min/1.73 m^2. However, there was incomplete recovery to baseline in more than half of the individuals. Predictors of renal recovery included a rapid decline in eGFR, concomitant use of a PI and shorter duration of TDF use. Renal function prior to TDF initiation did not predict greater recovery.[21]

Guidelines currently recommend the avoidance of TDF if the eGFR is <60 mL/min/1.73 m^2. In patients already on TDF who experience a >25% decline in eGFR from baseline or an eGFR <60 mL/min/1.73 m^2, substitution with an alternate antiretroviral agent is also recommended.[6,12,22]

Tenofovir alafenamide

Tenofovir alafenamide (TAF) is a prodrug of tenofovir. Discontinuation and switches from TDF to TAF have been associated with improved kidney function, though the long-term safety of TAF has not been established. In a pooled analysis of 26 clinical trials that included 9322 participants (TAF [n=6360] *versus* TDF [n=2962]) comparing the incidence of renal adverse events in adults and children, there were no reported cases of proximal renal tubulopathy in participants receiving TAF *versus* 10 cases in those receiving TDF ($p<0.001$).[23] There were also fewer individuals on TAF (3/6360) *versus* TDF (14/2962) ($p<0.001$) who discontinued these medications due to renal adverse events. This recent pooled analysis supports the renal safety of TAF over TDF, due to much lower plasma levels of tenofovir in these patients.[23]

Other NRTIs

The other NRTIs (stavudine, zidovudine, emtricitabine, abacavir [ABC] and lamivudine [3TC]) are considered 'renal friendly', but dose adjustment is required in the setting of renal failure, except for abacavir (Table 1). However, there are isolated case reports of abacavir causing acute interstitial nephritis (AIN) associated with systemic hypersensitivity reactions. Didanosine[24,25] and abacavir[26] have occasionally been associated with Fanconi syndrome and nephrogenic diabetes insipidus.

Non-nucleotide reverse transcriptase inhibitors

There have been isolated case reports of AIN in association with hypersensitivity reactions to the non-nucleotide reverse transcriptase inhibitor (NNRTI) efavirenz.[27] The other NNRTIs (nevirapine, etravirine or rilpivirine, doravirine) have not, to the authors' knowledge, been reported to have adverse effects on the kidney. No dose adjustments of the NNRTIs are required based on renal dysfunction (Table 1).

Protease inhibitors

Protease inhibitors (PIs) are convenient to use in renal dysfunction as dose adjustments are not required. However, clinicians need to be aware that there is a rare association with crystal nephropathy, interstitial nephritis and CKD.[6,28,29] The PIs indinavir and atazanavir, though rarely used, are insoluble in alkaline urine and promote crystalluria and occasionally crystal

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Table 1. ARVs and TB treatment use in renal dysfunction.

	CrCl (mL/min)			Haemodialysis (HD) (dose after dialysis)	Peritoneal dialysis	Continuous renal replacement therapy
	>50 (Usual adult dose)	10–50	< 10			
NRTIs						
Abacavir	600 mg daily or 300 mg twice daily	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Emtricitabine capsules	200 mg daily	30–49: 200 mg q48h 15–29: 200 mg q72h	< 15: 200 mg q96h	200 mg q96h	No data	No data
Emtricitabine oral solution	240 mg daily	30–49: 120 mg q24h 15–29: 80 mg q24h	< 15: 60 mg q24h	60 mg q24h	No data	No data
Lamivudine	300 mg daily or 150 mg twice daily	50–150 mg q24h	25–50 mg q24h	25–50 mg q24h	25–50 mg q24h	100 mg first day, then 50 mg q24h
Stavudine	30–40 mg twice daily	15–20 mg q12h	≥ 60 kg: 20 mg q24h < 60 kg: 15 mg q24h	≥ 60 kg: 20 mg q24h < 60 kg: 15 mg q24h	No data	30–40 mg q12h
Tenofovir disoproxil fumarate	300 mg daily	30–49: 300 mg q48h 10–29: 300 mg q72–96h	No data	300 mg q7d	No data	No data
Zidovudine	300 mg twice daily	No adjustment	100mg q8h or 300 mg daily	100 mg q8h or 300 mg daily	No data	300 mg q12h
NNRTIs						
Efavirenz, etravirine, nevirapine (NVP), rilpivirine, delavirine		No adjustment	No adjustment	No adjustment, except when on NVP patients should receive an additional dose of NVP 200 mg following each dialysis treatment	No adjustment	No adjustment
PIs						
Atazanavir (ATV), darunavir, fosamprenavir, lopinavir/ritonavir (LPV/r), ritonavir (r), nelfinavir, saquinavir, Tipranavir		No adjustment	No adjustment	No adjustment, except in ARV-experienced patients on HD: ATV and ATV/r are not recommended; also avoid once-daily dosing of LPV/r.	No adjustment	No adjustment

(*Continued*)

Table 1. (*Continued*)

	CrCl (mL/min)			Haemodialysis (HD) (dose after dialysis)	Peritoneal dialysis	Continuous renal replacement therapy
	> 50 (Usual adult dose)	10–50	< 10			
INSTIs						
Dolutegravir, raltegravir		No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Binding – Entry Inhibitors						
Enfuvirtide		No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Maraviroc		CrCl < 30: Without potent CYP3A inhibitors or inducers: 300 mg twice daily, reduce to 150 mg twice daily if postural hypotension occurs With potent CYP3A inhibitors or inducers: Not recommended		Without potent CYP3A inhibitors or inducers: 300 mg twice daily, reduce to 150 mg twice daily if postural hypotension occurs With potent CYP3A inhibitors or inducers: Not recommended	No data	No data
TB drugs						
Rifampicin	8–12 mg/kg q24h	300–600 mg q24h	300–600 mg q24h	300–600 mg q24h	300–600 mg q24h	300–600 mg q24h
Isoniazid	4–6 mg/kg q24h	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Ethambutol	15–25 mg/kg q24h	30–50: 15–25 mg/kg q24–36h 10–30: 15–25 mg/kg q36–48h	15 mg/kg q48h	15 mg/kg q48h	15 mg/kg q48h	15–25 mg/kg q24h
Pyrazinamide	25 mg/kg q24h	21–50: 25 mg/kg q24h 10–20: 25 mg/kg q48h	25 mg/kg q48h	25 mg/kg q48h	25 mg/kg q24h	25 mg/kg q24h

This table is not exhaustive. Antiretrovirals such as tenofovir alafenamide, bictegravir and elvitegravir that are only available as combination products have not been included.

This table was compiled using:

(i) Gilbert DN, Eliopoulos GM, Chambers HF, Saag, MS, Pavia, AT, eds. 2019. The Sanford guide to antimicrobial therapy 2019 [Electronic version]. Sperryville, VA: Antimicrobial Therapy, Inc.; 2019. https://webedition.sanfordguide.com/en. Accessed 21 October 2019.

(ii) Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. Downloaded from https://aidsinfo.nih.gov/guidelines on 22 October 2019.

ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleotide reverse transcriptase inhibitor; NRTI, nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; TB, tuberculosis.

nephropathy.[6,28] They have been linked to both interstitial nephritis and nephrolithiasis[30] and can progress to chronic interstitial nephritis and fibrosis with glomerulosclerosis.[29]

In a large study of 23,560 participants, there was a significant increase in CKD associated with each additional year of exposure to not only TDF but also ritonavir-boosted atazanavir (ATV/r) and ritonavir-boosted lopinavir (LPV/r). The reported adjusted incidence rate ratio for the three drugs were as follows: TDF 1.14 (95% confidence interval [CI]: 1.10–1.19), ATV/r 1.20 (95% CI: 1.13–1.26) and LPV/r 1.11 (95% CI: 1.06–1.16).[20]

Integrase strand transfer inhibitors

Integrase strand transfer inhibitors (INSTIs) require no dose adjustment in patients with renal dysfunction. However, dolutegravir (DTG) inhibits the tubular secretion of creatinine. The result is a rise in serum creatinine with a decrease in creatinine-calculated eGFR, which is not replicated when calculating the eGFR with inulin or cystatin C. Importantly, the effect is not pathological and is reversible.[31] For this reason, cystatin C is currently the preferred method to estimate eGFR in patients on DTG. Importantly, there is no dose reduction required in patients with impaired renal function.[32] The combination of elvitegravir, cobicistat, emtricitabine and TAF decreased the urine albumin:creatinine ratio, but there was a small rise in creatinine after switching from ABC/3TC and a third agent.[33]

Bictegravir is a second-generation INSTI that is available in combination with emtricitabine and TAF. There is minimal excretion of bictegravir in the urine, making it safe in renal impairment. Similar to DTG, there is a decrease in tubular secretion of creatinine resulting in an elevated serum creatinine, which is not indicative of a nephrotoxic effect.[34]

Entry inhibitors

The CCR5 antagonist, maraviroc, is available as a second-line agent. It does not form part of the WHO recommended ART regimen.[35] In the United States, it is an option to switch to maraviroc when there is virological failure.[36] Maraviroc is metabolised by cytochrome P450 3A4 (CYP3A4) and as such is susceptible to drug interactions. No dose adjustment is required in renal impairment, unless postural hypotension occurs.[37]

Single-tablet regimens

No single-tablet regimens (STRs) are currently approved for patients with HIV and ESRD on dialysis. Based on known pharmacokinetic properties, the STR ABC/3TC/DTG may represent a promising option. A recent retrospective case series reviewed the safety profile and efficacy of this combination. In this series, six PLWH on chronic haemodialysis were switched to the ART regimen containing ABC/3TC/DTG and had at least one set of virologic data before and after the switch. Only one patient demonstrated clinically significant resistance at baseline. Five patients (83%) achieved undetectable HIV-viral load after the switch. No decline in immune function was noted. ABC/3TC/DTG STR was well tolerated. Only one patient self-reported an adverse event (nausea), which resolved without drug discontinuation. ABC/3TC/DTG may be a safe and effective ART-STR option for patients with HIV and ESRD on haemodialysis. However, a larger trial, including a pharmacokinetic analysis, is needed to confirm these findings before this becomes the recommended STR.[38]

Recently, the combination of elvitegravir/cobicistat/emtricitabine/TAF has been shown to be safe in dialysis patients who were switched to this combination. Only 3 of the 55 patients switched to this combination developed treatment-related adverse events leading to this STR being discontinued. Ten patients had an unsuppressed HIV viral load at 48 weeks: one resuppressed, one had missing data with later data showing suppression, one had pre-existing resistance and the other seven were not on the STR at this time point (unrelated to virological failure).[39]

Polypharmacy in HIV and renal disease

Concomitant non-communicable diseases

There has been a rise in the prevalence of CKD worldwide. This has largely been driven by the increasing incidence of non-communicable diseases.[40,41] In Africa, it is no different[42] and compounded by epidemics of communicable diseases.[2] The commonest causes of CKD in SA are hypertension, glomerulonephritis, HIV and diabetes.[43] As there are 7.5 million (12.4%) people in SA living with HIV,[2] understanding the interactions between ART and the medications for the chronic diseases is essential. Table 2 provides interactions of ART with non-ART drugs that are commonly used in patients with HIV and concomitant illnesses.

Amlodipine

Amlodipine has a long elimination half-life of approximately 60 hours.[44,45] In the setting of HIV, ritonavir has been documented to significantly increase amlodipine plasma levels. The area under the curve (AUC) and maximum concentration (C_{max}) increase by approximately 90 and 89%, respectively. In a study of 18 healthy volunteers, the combination of amlodipine and ritonavir increased amlodipine exposure and decreased blood pressure; however, one subject developed nephrolithiasis.[46] The combination of efavirenz and amlodipine may be complicated by drug interactions, as amlodipine is metabolised by CYP3A4 and efavirenz induces this enzyme. To date, the authors are unaware of any formal pharmacokinetic studies on this combination.

Table 2. Examples of medicines that interact significantly with commonly used ART

Drug	Antiretroviral	Interaction and management
Aluminium hydroxide/ magnesium hydroxide	DTG	DTG forms insoluble complexes with metals (di- and tri-valent). Simultaneous coadministration of aluminium-containing antacids with DTG (50 mg once daily) decreased DTG C_{max}, AUC and C_{trough} by 72, 74 and 74%, respectively. Antacid should be taken a minimum of 2 hours after or 6 hours before dolutegravir. Avoid combination in the presence of integrase class resistance.
	LPV/ATV/DRV + r	ATV solubility/absorption decreases as pH increases. ATV should be administered 2 hours before or 1 hour after antacids.
	RAL	Decreased RAL exposure. Do not coadminister.
	RPV	RPV plasma concentration decreases as the pH increases. Administer antacids 2 hours before or 4 hours after RPV.
Amikacin/ kanamycin/ amphotericin B	TDF	Potential for additive nephrotoxicity. Avoid concurrent use if possible or monitor renal function weekly if concurrent use unavoidable.
Amlodipine	LPV/ATV/DRV + r	Amlodipine levels significantly increased by PIs. Both ATV and calcium channel blockers can prolong PR interval. Use with caution. If coadministration is indicated, consider a dose reduction for amlodipine of 50%. ECG monitoring is recommended.
Bedaquiline	EFV	Models predict that long-term use of EFV could decrease bedaquiline AUC by 50%. Also, additive risk of QT prolongation. Avoid combination.
	ETR	No data available, but ETR may reduce bedaquiline exposure due to induction of CYP3A4. Avoid combination until more data available.
	LPV/ATV/DRV + r	A 2- to 3-fold increase in the exposure of bedaquiline is expected with LPV/r. No data for other PIs, but similar interaction expected. Clinical significance is unknown, monitor ECG and LFTs monthly.
Calcium salts/ ferrous salts	DTG	DTG forms insoluble complexes with metals (di- and trivalent). If taken with food, this interaction is not clinically relevant. Take DTG and supplement with food or take the calcium/iron supplement a minimum of 2 hours after or 6 hours before dolutegravir.
	LPV/ATV/DRV + r	Calcium-containing products used as antacids may reduce plasma concentrations of ATV. Administer atazanavir 2 hours before or 1 hour after calcium-containing products used as antacids.
	RAL	RAL binds to divalent cations such as calcium/iron and forms a complex at the level of the gastrointestinal tract, which results in less raltegravir being absorbed. Separate doses by at least 4 hours.
	RPV	Calcium products used as antacids increase gastric pH and may lead to decreased RPV plasma concentrations. Administer antacid at least 2 hours before or 4 hours following RPV administration.
Carbamazepine/ phenobarbitone/ phenytoin	DTG	**Carbamazepine:** Coadministration of carbamazepine and DTG (50 mg once daily) decreased DTG C_{max}, AUC and C_{min} by 33, 49 and 73%, respectively. Use DTG 50 mg twice daily in treatment-naive or treatment-experienced patients but integrase inhibitor-naive. Avoid combination when integrase inhibitor resistance suspected. **Phenobarbitone/phenytoin:** Decreased DTG concentrations expected due to induction of UGT1A1 and CYP3A by phenobarbital/phenytoin. Avoid combination. Safer alternatives include lamotrigine and levetiracetam.
	EFV	When EFV is administered concomitantly, there is a reduction in the plasma concentrations of both drugs. Avoid combination. Valproic acid (contraindicated in pregnancy and women of childbearing age), lamotrigine or levetiracetam can be used as an alternative.
	ETR	Reduced plasma concentrations of ETR. Avoid combination. Valproic acid (contraindicated in pregnancy and women of childbearing age), lamotrigine or levetiracetam can be used as an alternative.

(*Continued*)

Table 2. (*Continued*)

Drug	Antiretroviral	Interaction and management
	LPV/ATV/DRV + r	Coadministration may result in decreased concentrations of protease inhibitors. Also, PIs may increase the levels of carbamazepine and decrease phenytoin concentrations. Avoid combination. Valproic acid (contraindicated in pregnancy and women of childbearing age), lamotrigine (may require higher dose) or levetiracetam can be used as an alternative to carbamazepine.
	NVP	NVP may cause decreased carbamazepine plasma concentrations. Also, carbamazepine, phenytoin and phenobarbitone may lower NVP concentrations. Avoid combination. Valproic acid (contraindicated in pregnancy and women of childbearing age), lamotrigine or levetiracetam can be used as an alternative.
	RAL	Theoretically, RAL concentrations may be reduced via induction of glucuronidation. Consider therapeutic drug monitoring for RAL or monitor antiviral efficacy closely.
	RPV	Theoretically, RPV concentrations may be reduced via induction of CYP3A. Avoid combination.
Cimetidine/ ranitidine	LPV/ATV/DRV + r	No clinically significant interaction with LPV/DRV/r, but significantly reduces absorption of atazanavir. Atazanavir: management complicated and dependent on ARV regimen and dose of cimetidine/ranitidine.
	RPV	Coadministration may decrease RPV concentrations due to decreased absorption. Use H2 antagonists that can be dosed once daily and take it at least 12 hours before or 4 hours after RPV.
Contraceptives, oral	EFV	EFV did not change ethinylestradiol (EE) AUC, but significantly reduced exposure to the active metabolites of norgestimate. In another study, levonorgestrel levels were significantly reduced. Coadministration is expected to reduce contraceptive efficacy of desogestrel and EFV concentrations decreased by 22%. Use with caution. Avoid low-dose oral contraceptives (<35 mcg of EE). High-dose oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used.
	LPV/ATV/DRV + r	Ethinylestradiol (EE) AUC decreased by 42% and norethisterone concentration also decreased by LPV/r. Unboosted ATV may increase EE levels. ATV boosted with ritonavir decreased EE levels. DRV decreased EE AUC by 44%. Use with caution. LPV/ATV/DRV + r: Avoid low-dose OCs (<35 mcg of EE). High-dose oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used. ATV (unboosted): use no more than 30 mcg EE.
	NVP	Ethinylestradiol and norethisterone AUCs are decreased by 29 and 18% respectively by NVP. Use with caution. Avoid low-dose OCs (<35 mcg of EE). High-dose oral or injectable contraceptive or IUD are options. In addition, a barrier method must be used. Subsequent research has demonstrated no significant difference in ovulation and pregnancy rates.
Diazepam	EFV	Conflicting data on whether EFV is predicted to increase/decrease diazepam exposure. Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
	ETR	Conflicting data on whether ETR is predicted to increase/decrease diazepam exposure. Alternatives to diazepam should be considered. Lorazepam, oxazepam or temazepam are safer alternatives.
	LPV/ATV/DRV + r	Unpredictable. Avoid combination. Lorazepam, oxazepam or temazepam are safer alternatives.
	NVP	Theoretically, NVP may reduce diazepam levels. Monitor for diazepam effects, and withdrawal symptoms when adding NVP to patient already on diazepam.
Esomeprazole/ lansoprazole/ omeprazole	LPV/ATV/DRV + r	ATV: 75 and 94% decrease in AUC of ATV with omeprazole and lansoprazole, respectively. Coadministration of ATV and proton pump inhibitors is generally not recommended. If unavoidable, consider increasing ATV dose to 400 mg daily with ritonavir 100 mg daily and limiting the PPI dose to the equivalent of 20 mg omeprazole.

(*Continued*)

Table 2. (*Continued*)

Drug	Antiretroviral	Interaction and management
	RPV	Decreased RPV concentrations due to reduced absorption of RPV as a result of an increase in gastric pH. Avoid combination.
Etonogestrel	EFV	Coadministration decreases etonogestrel levels due to induction of CYP3A4. Increased risk of pregnancy has been reported. Contraindicated.
	ETR	Coadministration is predicted to decrease etonogestrel levels due to induction of CYP3A4. Use another method of contraception.
Fluticasone	LPV/ATV/DRV + r	Increased fluticasone levels possibly resulting in decreased plasma cortisol concentrations (e.g. Cushing's syndrome, adrenal suppression). Avoid combination. Safer alternative is beclomethasone.
Itraconazole	EFV	Itraconazole effects decreased. In addition, increased risk of QT interval prolongation in some patients, for example, slow metabolisers of efavirenz. Avoid concurrent use.
	ETR	ETR is predicted to decrease itraconazole concentrations, and itraconazole is expected to increase ETR plasma concentrations. Use with caution.
	LPV/ATV/DRV + r	Effects of both itraconazole and PIs may be increased. High doses of itraconazole (greater than 200 mg/day) are not recommended. Monitor for toxicity. Suggested alternative is fluconazole or terbinafine.
	NVP	Itraconazole levels reduced. Do not coadminister.
	RPV	Potential increase in RPV concentrations. Ketoconazole AUC decreased 24% by 150mg RPV. No dosage adjustment required. Monitor clinical effect of antifungal.
	TDF	Tenofovir-DF absorption may be increased via P-glycoprotein inhibition. Monitor renal function frequently, when using tenofovir-DF.
Metformin	DTG	DTG increases metformin AUC by 79% (once daily) – 145% (twice daily). If concomitant use is needed, limit total daily dose of metformin to 1000 mg when starting metformin or DTG. Monitor renal function and blood glucose when starting and stopping.
Rifabutin	EFV	Decreased rifabutin effects. Increase rifabutin to 450 mg/day or 600 mg three times per week with concomitant EFV.
	ETR	ETR AUC decreased by 37%. No dosage adjustment required, unless coadministered with a boosted PI. With boosted PI: caution and monitoring recommended and the US guidelines suggest ETR and rifabutin should not be coadministered with boosted DRV, LPV or saquinavir.
	LPV/ATV/DRV + r	Significantly increased rifabutin levels. Reduce rifabutin dose to 150 mg daily and monitor for adverse events such as neutropenia and uveitis.
	RPV	RPV AUC decreased by 42%. Increase RPV dose to 50 mg once daily.
Rifampicin	DTG	Decreased DTG concentrations due to induction of UGT1A1 and CYP3A by rifampicin. If no integrase inhibitor mutations present, increase DTG dose to 50 mg twice daily. Avoid DTG if integrase inhibitor mutations present.
	ETR	Decreased ETR concentrations. Contraindicated.
	LPV/ATV/DRV + r	Rifampicin reduces ATV, DRV and LPV levels. Increases in ALT/AST. Dosage adjustment required in resource-limited settings where rifabutin not readily available: Adults: The dose of LPV/r should be doubled slowly over 2 weeks (to 800/200 mg twice daily). Monitor ALT while increasing the dose at weekly intervals, and then monthly while on double dose. Children: Extra ritonavir should be added at a dose of 0.75 x the volume of the LPV/r dose. Avoid concurrent use with ATV/r and DRV/r as dose adjustment not established. Consider rifabutin 150mg daily as an alternative.
	NVP	Decreased NVP levels (AUC decreased by 58%). Switch to another ARV, if possible. If switch not possible, then consider monitoring trough NVP levels and adjusting dose accordingly. Monitor liver function closely.

(*Continued*)

Table 2. (*Continued*)

Drug	Antiretroviral	Interaction and management
	RAL	RAL AUC and minimum plasma concentration decreased by 40 and 61%, respectively. Although the manufacturer states that doubling of RAL dose to 800 mg twice daily can be considered, a clinical trial has shown that a dose adjustment may not be necessary. Monitor virological response closely. No data in children.
	RPV	RPV AUC decreased by 80%. Contraindicated.
Simvastatin	EFV	EFV significantly reduces the concentrations of simvastatin. Patients should be closely monitored for antilipid activity and the simvastatin dose may need to be increased.
	ETR	Decreased simvastatin exposure. Monitor response. Dose adjustments for simvastatin may be needed.
	LPV/ATV/DRV + r	Significantly increased simvastatin levels. Do not coadminister due to an increased risk of myopathy including rhabdomyolysis. Low-dose atorvastatin (max 10 mg/day) or pravastatin are alternatives.
	NVP	Potential for decreased concentrations of simvastatin due to enzyme induction by NVP. Patients should be closely monitored for antilipid activity, and the simvastatin dose may need to be increased.
	RAL	Additive risk of myopathy and rhabdomyolysis. Use with caution.

This table has been compiled using: HIV-druginteractions.org. Liverpool HIV interactions. 2019. https://www.hiv-druginteractions.org. Accessed August–November 2018; Preston C, ed. *Stockley's Drug Interactions*. 11th ed. Italy: Pharmaceutical Press; 2016; NCBI.nlm.nih.gov. Home – PubMed – NCBI. 2019. https://www.ncbi.nlm.nih.gov/pubmed. Accessed August–November 2018; Micromedexsolutions.com. DRUGDEX detailed drug information. 2019. http://www.micromedexsolutions.com. Accessed August–November 2018.
AUC, area under the curve; RAL, raltegravir; EFV, efavirenz; ETR, etravirine; LPV, lopinavir; ATV, atazanavir; DRV, darunavir; r, ritonavir; NVP, nevirapine; RPV, rilpivirine; DTG, dolutegravir; TDF, tenofovir;

Simvastatin

Simvastatin is extensively metabolised by CYP3A4. Ritonavir is an inhibitor of CYP3A4. Fichtenbaum and colleagues observed a dramatic increase in simvastatin plasma concentration (approximately 30-fold) in the presence of ritonavir plus saquinavir in HIV-negative volunteers. There were also reports of rhabdomyolysis with this drug combination. For atorvastatin, the concentration increase was less than for simvastatin, but significant at 347%.[47] In clinical practice, the use of simvastatin and ritonavir is contraindicated due to severe adverse events. Therefore, dose-adjusted atorvastatin (10–20 mg per day)[48] or pravastatin are the preferred statins in the presence of ritonavir.[49]

Gerber and colleagues demonstrated that efavirenz significantly reduced simvastatin, atorvastatin and pravastatin levels. There was no effect of any of these statins on efavirenz pharmacokinetics.[49] When 40 mg simvastatin was combined with efavirenz 600 mg in healthy individuals, there was a median decline of about 58% in the AUC and 50.5% of the C_{max} for simvastatin. Furthermore, the low density lipoprotein (LDL) decline when efavirenz and simvastatin were combined was significantly less than with simvastatin alone.[49] There is probably no major drug interaction between nevirapine and any of the available statins.[50]

Concomitant opportunistic infections

Opportunistic infections are common, with MTB being declared a global health emergency and the leading cause of death from a single infectious agent.[14] It is the ninth leading cause of death worldwide.[14] Three-quarters of the HIV-associated MTB cases occur in Africa.[13] The drug interactions with MTB/HIV co-infection are important to understand.

Tuberculosis therapy

MTB is the commonest opportunistic infection globally in PLWH.[51] Curative treatment requires prolonged drug therapy and may expose patients to drug-induced toxicities. These include, among others, drug-induced hepatitis, skin rash and peripheral neuropathy. Many co-infected patients present for the first time with advanced immunosuppression and require ART initiation during MTB treatment, with the risk of drug–drug interactions and overlapping toxicities. The standard treatment for drug-sensitive MTB includes rifampicin, isoniazid, ethambutol and pyrazinamide over a 2-month intensive phase followed by a continuation phase with rifampicin and isoniazid for 4 months.

Toxicities may occur in up to 80% of patients, with the most common being hepatoxicity.[52] Renal involvement has

been reported as rare. The most common offending drug is rifampicin, where AKI has been documented in 0.1% of patients.[53] Rifampicin-induced nephrotoxicity most commonly arises when rifampicin is administered intermittently.[54,55] Discontinuation of rifampicin reportedly results in 96% of patients achieving full recovery within 90 days.[54] AKI is postulated to be the result of immunologically mediated tubulointerstitial injury. Anti-rifampicin antibodies are produced after re-exposure to the antigen and cause target-cell damage after complement activation.[56] These patients must never receive rifampicin in the future.

Isoniazid is not routinely considered nephrotoxic. However, there have been isolated reports of the development of metabolic acidosis with deterioration in renal function in patients with underlying impaired renal function.[57] CKD may also increase the risk of isoniazid-induced neuropathies.[58]

Ethambutol is mostly excreted in the urine unchanged and requires dose adjustment in renal insufficiency (Table 1).[59] There is a dose-dependent risk of retrobulbar neuritis, which may be reversible with early cessation of ethambutol therapy.[60]

In the setting of MTB resistance to rifampicin or isoniazid, the WHO recommends the following drugs in various combinations, as alternative therapy: bedaquiline, moxifloxacin, amoxicillin-clavulanic acid, clofazimine, ethambutol, levofloxacin, streptomycin, cycloserine/terizidone, capreomycin, pyrazinamide, ethionamide, amikacin, kanamycin, p-aminosalicylic acid, thioacetazone, delamanid or linezolid. Of these agents, streptomycin, kanamycin, capreomycin and amikacin are all recognised nephrotoxins and, where possible, should be avoided. If required in the presence of renal dysfunction, they should be appropriately dose adjusted. With respect to amikacin, Sagwa *and colleagues* showed no difference in adverse events after exposure to amikacin (specifically tinnitus and hearing loss), when comparing patients with and without HIV.[61] However, this study did not report the underlying renal function.

Antibiotics and antifungals in HIV

In 2010, the sub-Saharan African mortality rates during the first year of ART were very high (8–26%). This was higher than the rates reported in the Caribbean and Latin America (3–13%) and in South-East Asia (11–13%). This was likely due to lower cluster of differentiation 4 (CD4) counts on initiation of ART in Africa. The five leading causes of early morbidity on ART initiation include MTB, acute sepsis, cryptococcal meningitis, malignancy and wasting syndrome/chronic diarrhoea. The causes of sepsis were predominantly episodes of pneumonia, bacteraemia, enteritis and pyelonephritis, and the most commonly isolated pathogens were *Streptococcus pneumoniae*, non-typhoidal *Salmonella* and *Escherichia coli*.[62,63] The majority of these diseases require treatment with antibiotics.

Prescribers must be cognisant of the 100-fold increased risk of immune-mediated adverse drug reactions in PLWH, which may present as AKI.[64] This has been attributed to a dysregulated immune system. The increased susceptibility to immune-mediated drug reactions is based on genetic susceptibility, CD4 depletion, co-infections, metabolic disturbances and certain drug factors, including immunogenicity, polypharmacy and intermittent drug use.[64]

Antibiotics that have been proven to cause hypersensitivity reactions are beta lactams, macrolides, co-trimoxazole, quinolones and dapsone. Vancomycin is less nephrotoxic than previously thought, but in the setting of HIV, case reports have documented increased susceptibility to renal dysfunction. One case report illustrates how lack of muscle mass impairs the ability to accurately assess vancomycin-associated AKI.[65]

Co-trimoxazole

The combination of trimethoprim and sulfamethoxazole is widely used in PLWH. Its value is advocated for both prophylaxis and treatment of *Pneumocystis jirovecii,* urinary tract infections and other organisms to which severely immunocompromised individuals are susceptible. Documented cases of renal dysfunction have been reported and are caused by a number of mechanisms.[66] Trimethoprim impairs potassium and creatinine tubular secretion, resulting in the appearance of renal dysfunction and hyperkalaemia. The elevated creatinine levels are not a true reflection of glomerular filtration and rapidly return to normal with cessation of the drug. However, the hyperkalaemia can be responsible for its known complications, including arrhythmias and palpitations, weakness, chest pain, dyspnoea and nausea. A 50% dose adjustment is recommended if the eGFR is <30 mL/min/1.73 m^2, which improves the renal safety.[59]

Sulfamethoxazole, as with all sulphonamides, can cause hypersensitivity reactions resulting in the development of tubulointerstitial nephritis, which may be rapid in onset and associated with granulomatous inflammation.[59,67,68] These reactions have been found to be more frequent in patients with HIV, with those having uncontrolled disease being particularly at risk.[69]

Amphotericin B

The antifungal activity of amphotericin B is limited by dose-related toxicity. It is frequently used in the setting of HIV as it effectively treats cryptococcal infection. Amphotericin is highly bound to lipoproteins and has an extremely long elimination half-life of 15 days. Nephrotoxicity is dose dependent and ranges from 12 to 53% in treated patients. It may be related to an infusion reaction or vasoconstrictive effects, particularly to the afferent arteriole.[70] LDL receptors in the proximal and distal

renal tubules have a high affinity for amphotericin B leading to tubular toxicity. The tubular defects that are described are renal tubular acidosis, concentrating defects and electrolyte disorders.[70] Lipid-based formulations of amphotericin B preferentially bind to high density lipoprotein (HDL; over LDL), which explains, in part, their lower nephrotoxicity. The presence of amphotericin-induced AKI is a predictor of acute dialysis and mortality.[70] In a study of patients prescribed amphotericin B, whose creatinine rose above 221 μmol/L, 38% required dialysis and there was a three-fold increase in mortality.

Renal-specific diseases

Immunosuppression

Encouraged by earlier, small, non-randomised studies suggesting a benefit of corticosteroids for the treatment of HIV-associated nephropathy (HIVAN),[71] Wearne and colleagues performed a randomised controlled trial to assess the effect of corticosteroids in naive patients initiated on ART. Twenty-one patients were randomised to ART plus 1 mg/kg of corticosteroids for 6 months and 17 patients to ART alone. The study demonstrated a statistically significant improvement in median eGFR from baseline to last follow-up with those in the corticosteroid arm (i.e. Δ=25 mL/min [interquartile range [IQR]: 15–51] *versus* 9 mL/min [IQR: 0–24], $p = 0.008$). However, there were eight deaths in the corticosteroid arm, and due to this high mortality, routine use of corticosteroids cannot currently be recommended.[72]

In contrast to these findings, a study conducted in South Africa and other African countries, initiated corticosteroids for 6 weeks for the adjuvant treatment of tuberculous pericarditis using substantially higher doses of corticosteroids compared with the earlier-mentioned study. Prednisolone was initiated at 120 mg daily, with weekly tapering to 90 mg, then 60 mg, 30 mg, 15 mg and 5 mg. Two-thirds of the patients enrolled in this study were infected with HIV. The study demonstrated a significant reduction in the incidence of constrictive pericarditis with no increased risk of mortality in those patients receiving corticosteroids. The trial did however demonstrate an increase in HIV-associated cancers, a finding not observed in the 2 years of follow-up in the HIVAN study.[73]

Immunosuppression has been used for the treatment of large vessel vasculitis (LVV) in HIV. One study retrospectively reviewed 93 cases, 11 of which were HIV infected. Five of the 11 patients received corticosteroids and two received azathioprine and methotrexate. One patient, who did not receive immunosuppression, died in the 96 months of follow-up. Traditionally, patients with HIV-associated vasculitis are less likely to be prescribed corticosteroids than patients without HIV.[74] However, due to the severity of LVV in HIV-infected patients, corticosteroids are recommended to avoid vascular complications in this group.[74]

Granulomatous interstitial nephritis

There appears to be a rise in the prevalence of GIN in the setting of HIV. GIN is a variant of AIN where granulomas are seen in the interstitium of the kidney. Granulomas develop in response to predominantly macrophage and T cells being activated by a persistent stimulus.[75] The current international literature reports GIN to occur in 0.5–1.37%.[76,77] However, in a HIV-positive renal biopsy series from SA, the prevalence of GIN was 10–29 times higher than this, with 14.2% of biopsies demonstrating GIN.[15]

Drugs, infections, inflammatory conditions and various malignancies have been linked to the aetiology of GIN; however, the causes are region specific.[15,78] In a HIV-positive cohort from SA, MTB was the leading cause, with drugs coming in second. Internationally, drugs or sarcoidosis remain the most common causes of GIN.[75] The usual drugs implicated in GIN remain implicated in HIV. The drugs implicated in a recent HIV-positive biopsy series were cotrimoxazole, antibiotics, non-steroidal anti-inflammatory drugs and diuretics.[15] In the presence of HIV, the histological picture also varies. There is an entity of 'ill-formed granulomas' described in the setting of advanced AIDS.[79] It has been documented in the presence of drug-induced GIN but has also been seen in other organs.[75] Another observation is the development of granulomas in patients with immune reconstitution inflammatory syndrome (IRIS) with the introduction of ART.[80–82]

Recommendations for prescribing in the setting of HIV and renal disease

ART in the setting of renal dysfunction

AKI and HIV

In the developing world, AKI in PLWH is common.[82] AKI may develop due to hypovolaemia, sepsis, MTB and the use of nephrotoxic drugs. Glomerular disease can also manifest as AKI.[4,83,84] AKI in hospitalised patients has a high risk of mortality, even after the initiation of ART.[85] Numerous centres from SA report on outcome data of PLWH receiving renal replacement therapy (RRT) for AKI. The reported mortality rates range between 44 and 60%.[3,86,87] Reported AKI rates in SA are higher than first-world HIV-positive cohorts. In 2013, the incidence of AKI in SA was reported as 5.9 per 100 patient years in ambulatory patients and ~18% in hospitalised HIV-infected patients.[86] This is compared to a very low reported incidence of AKI in first-world HIV-positive cohorts (0.77 [95% CI: 0.45–1.33]/1000 patient years).[88]

An approach to AKI management in HIV should include all conservative measures outlined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for AKI for prevention and supportive care.[89] Additional measures that

must be considered in the setting of HIV include: (i) stopping nephrotoxic agents including TDF, (ii) changing to alternative renal 'friendly' options (e.g. abacavir) and (iii) dose adjustment of NRTIs based on eGFR. Once renal recovery is present, NRTI doses must be readjusted.[90] In a study from SA, TDF was stopped on admission in all patients with AKI. At 3-month follow-up, 55 patients (31%) had been restarted on full dose TDF-based ART without apparent adverse effects, 38 (22%) of whom had been TDF-exposed on admission.[91] An aggressive search for occult sepsis or MTB must be performed, as sepsis is a common cause of renal dysfunction. MTB associated with AKI carries a high mortality.[92]

In ART naive patients, ART should be initiated after recovery from AKI and after stabilisation of treatment of opportunistic infections (MTB and cryptococcal). This should occur at 3 months to monitor renal function and review the need for dose adjustments.[89]

Initiation of ART in the setting of CKD

HIV treatment guidelines recommend a test-and-treat approach. That is, ART should be initiated in all PLWH, irrespective of CD4 count. This strategy aims not only to improve mortality and prevent opportunistic infections, but also to reduce the incidence of both AKI and HIV-related kidney diseases.[93] The SA national protocol dictates that first-line therapy consists of TDF/3TC and DTG or efavirenz. This is given as an STR. The presence of CKD affects the choice and dosing of renally cleared antiretroviral agents. Renal function, presence of proteinuria and CKD risk factors should be assessed prior to ART initiation and then at 3 months and 6 months.[6,90] Once the patient is stable on ART, patients should have an annual renal function assessment with quantification of proteinuria.

The recommendations further state that all patients, regardless of initial renal function, on potentially nephrotoxic ART (TDF in any combination, but particularly with ritonavir or cobicistat) or at high risk of CKD (eGFR <70 mL/min, urine protein creatinine ratio >500 mg/g, >60 years, comorbidities: diabetes, hypertension, hepatitis C virus infection or cardiovascular disease) should be closely monitored. The recommended monitoring in these patients is prior to ART initiation, at 1 month and then 6 monthly. In the situation where patients are hospitalised or on concomitant nephrotoxins, renal function should be monitored more closely. If TDF is used with ritonavir or cobicistat, then 3–6 monthly monitoring is suggested along with serum phosphate and urinalysis.[6]

The WHO updated the recommendations for ART in July 2019.[35] First-line ART regimens are DTG /NRTI backbone or efavirenz/ NRTI backbone in adults. STR is available for these regimens, but the NRTIs require dose adjustment in renal dysfunction or are not recommended in renal impairment. In the United States, the guidelines for ART recommend against the use of TDF if the eGFR is <60 mL/min/1.73m^2, and the recommended combinations all require dose adjustment in the setting of impaired renal function.[36]

ART in the setting of RRT

Dose adjustment of ART is essential in patients with CKD or on RRT. Fixed-dose combinations are not recommended once eGFR is < 60 mL/min/1.73 m^2. Incorrect dosing has been linked to increased mortality.[94] Table 1 summarises the dosage adjustments required for ART. The South African recommendations for initiating a patient on ART with CKD on dialysis is abacavir 600 mg, 3TC 50 mg first dose and then 25 mg daily and efavirenz 600 mg every night.[90] Dosing should be after haemodialysis because the NRTIs are eliminated by dialysis.

ART in transplantation

The interaction between ART and immunosuppressive drugs has introduced challenges in the area of transplantation in HIV-positive individuals. There are significant drug–drug interactions that influence management. Ritonavir is an inhibitor of the cytochrome P450 enzyme system that significantly inhibits the metabolism of tacrolimus, decreasing its clearance by 80%. This leads to an increase in the AUC by a factor of 5.[95] Patients therefore require substantial tacrolimus dose reductions, with regular plasma therapeutic drug monitoring. Dosing may only need to occur once every 7–10 days to maintain adequate plasma levels. In contrast, the NNRTIs, efavirenz and nevirapine, induce the cytochrome P450 enzyme system, increasing the metabolism of tacrolimus, necessitating much higher doses. This can have dramatic cost implications. However, apart from cost implications, drug interactions have significant clinical implications. In the landmark study by Muller and colleagues, which describes HIV-positive donor to HIV-positive recipients, patients who received ritonavir-based ART had a higher incidence of calcineurin-inhibitor nephrotoxicity seen on renal biopsy than patients who received NNRTIs. Rejection rates have also been reported to be approximately 2–3 times higher than those among HIV-negative recipients.[96,97] It has been hypothesised that immune dysregulation and the challenge of managing the drug interactions between the ART and immunosuppressants are responsible for these rates.

Conclusion

In the setting of HIV, drug toxicities commonly occur. The causes are multifactorial and include patient and HIV-related factors, opportunistic infections, polypharmacy and drug interactions. Kidney injury is often a complication of drug toxicity, and impaired renal function complicates drug administration. This review has attempted to highlight common drugs used in the setting of HIV, how they affect and are affected by the kidney as well as their risk of nephrotoxicity. Tables have been created, for ease of reference, demonstrating dosage adjustments and major drug interactions. A practical approach is provided for dose adjustment in the setting of renal impairment, including dialysis.

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