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Renal Tubular Transporter-Mediated Interactions of HIV Drugs: Implications for Patient Management

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Abstract

Interactions of drugs with renal transporters can reduce the tubular secretion of endogenous products and affect drug pharmacokinetics, efficacy, and toxicity. This review aims to understand the clinical implications of renal transporter-mediated interactions of HIV drugs. These interactions have been fully investigated for nucleoside/nucleotide reverse transcriptase inhibitors, particularly tenofovir disoproxil fumarate, and for some of the newer agents, such as rilpivirine, dolutegravir, and cobicistat. Interactions may include competition, inhibition, or induction of transporters, and interference with renal active secretion of creatinine, the most commonly used marker of renal function. Drug-drug interactions may result in an increased risk of drug toxicity. This interaction is more likely to occur with the protease inhibitors, particularly ritonavir, due to the inhibitory effects of these drugs on specific transporters involved in renal excretion of other drugs. Interactions with the transport of creatinine have been identified with rilpivirine, dolutegravir, and cobicistat. While rilpivirine and dolutegravir inhibit mainly the renal transporter OCT2 in the basolateral membrane of the proximal tubular cell, cobicistat predominantly inhibits the renal transporter MATE1 in the luminal membrane. These interactions can cause mild-to-moderate increases in serum creatinine concentrations and moderate reductions in estimated glomerular filtration rate that do not translate into real decreases in glomerular filtration. To use these drugs safely, clinicians must correctly interpret changes upon initiation of therapy to differentiate these spurious elevations in serum creatinine from clinically significant toxicity. In this article we propose a set of recommendations for clinical use of antiretroviral drugs that interfere with creatinine renal transporters. **(AIDS Rev. 2014;16:199-212)**

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Key words

Antiretroviral therapy. Kidney. Renal function. Renal toxicity. Creatinine. HIV. AIDS.

Introduction

Cellular membrane transporters play a key role in facilitating transmembrane drug movement. In particular, drug transporters in the kidney can considerably influence the pharmacokinetics and clinical effects of several drugs, including antiretroviral agents[1,2]. Renal transporters are also essential for tubular secretion of creatinine, the most commonly used marker of renal function in clinical practice[3,4].

Interactions of antiretroviral drugs with renal transporters have been fully investigated for nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), particularly tenofovir disoproxil fumarate (TDF), and for some of the newer antiretroviral drugs, such as rilpivirine (RPV), dolutegravir (DTG), and cobicistat (COBI)[5-9]. Tenofovir is eliminated by the kidneys through a combination of glomerular filtration and tubular secretion via organic anion and multidrug-resistant

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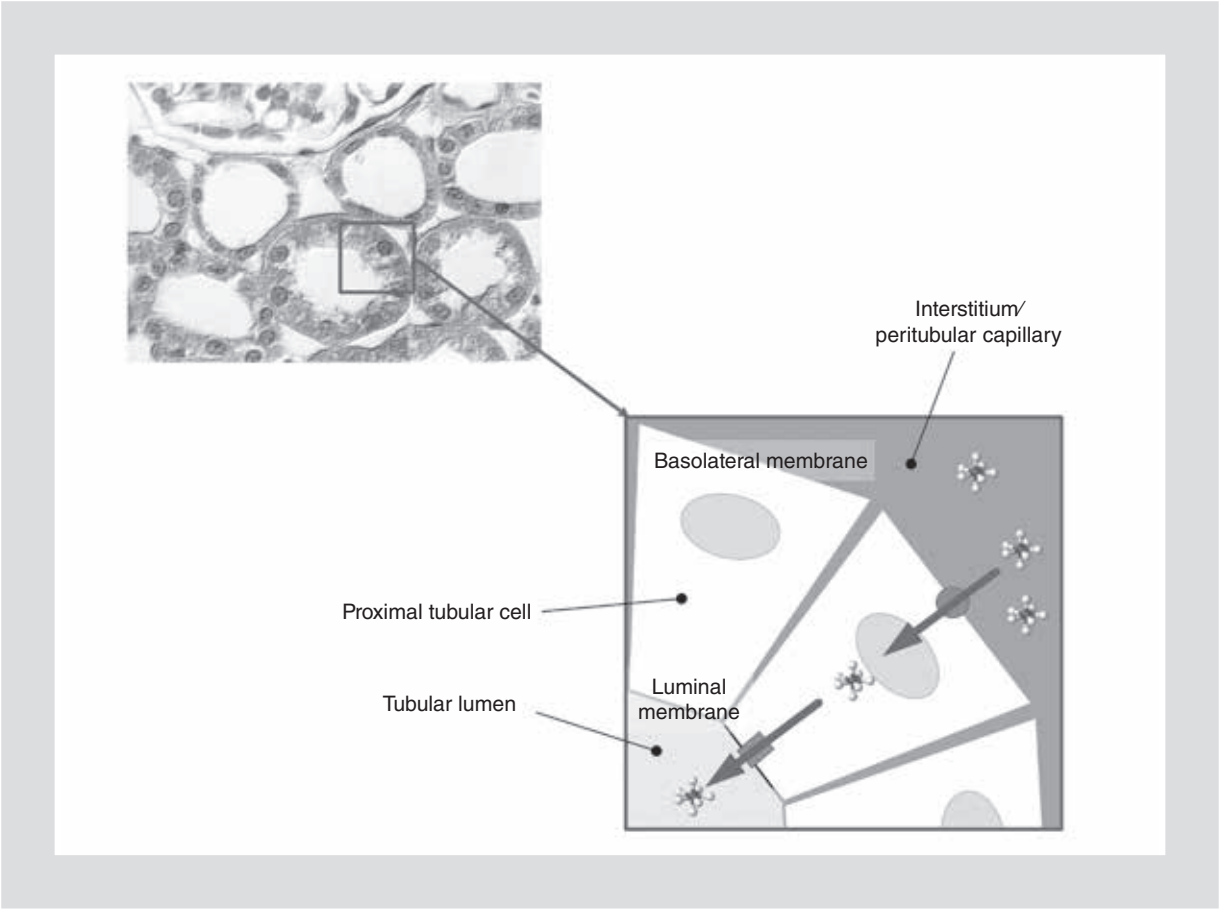

Figure 1. *Proximal tubular epithelial cells and schematic representation of the process of tubular secretion.*

protein transporters[5,10,11]. Rilpivirine, DTG, and COBI interact with various renal transporters, resulting in a measurable decrease in the tubular secretion of creatinine and non-progressive increases in serum creatinine[7-9,12,13]. In contrast, limited data have been published on interactions with other commonly used antiretrovirals, including first-generation nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI)[2,14,15].

In this article we review renal membrane transporters, focusing on the potential of antiretroviral agents to cause interactions, and discuss the clinical implications of these interactions for patient management.

Renal tubular membrane drug transporters: physiologic role

The kidney plays a critical role in the elimination of endogenous waste products generated during cellular metabolic processes of multiple exogenous substances (xenobiotics) that enter the body, including drugs or environmental toxins in their primary form or as metabolites. Renal clearance involves three basic mechanisms in different segments of the nephron: free glomerular filtration, tubular reabsorption of some filtered elements, and active tubular secretion of non-filtered substances from the peritubular capillary and the surrounding interstitial space.

The proximal tubule, particularly its convoluted portion, is one of the main sites in which much of tubular secretion and marked reabsorption takes place. Proximal tubular epithelial cells form a monolayer lining the inner wall of the tubule that enables contact between the peritubular space formed by the interstitium/peritubular capillaries and the tubular lumen. In the proximal tubular cell, we can distinguish the basolateral membrane that is in contact with the interstitium and peritubular capillaries, and the luminal membrane exposed to the tubular lumen as a tall brush border that considerably increases the surface of interchange (Fig. 1).

Given that cell membranes are lipophilic and therefore impermeable to hydrophilic and ionic substances,

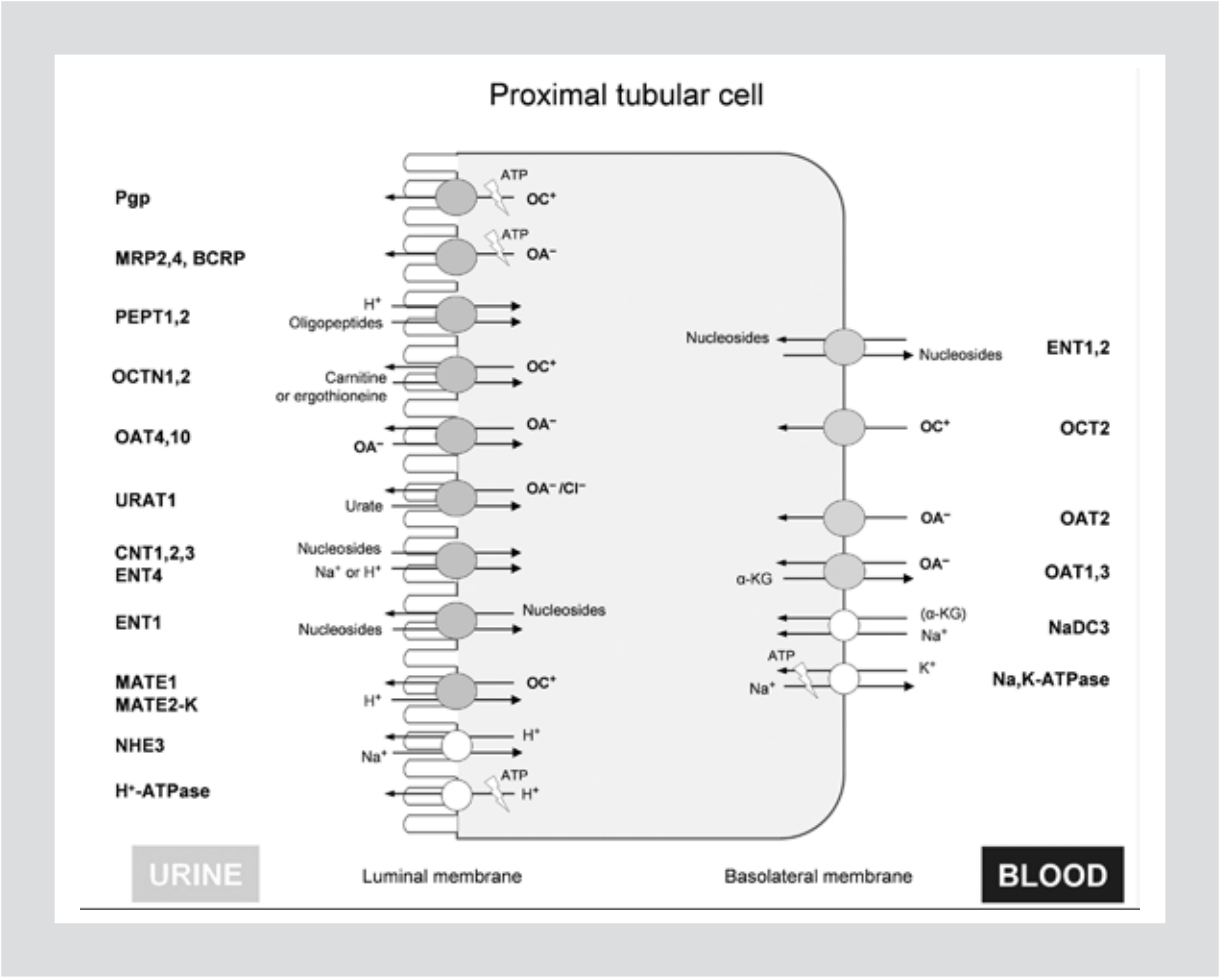

Figure 2. *Main renal tubular membrane drug transporters. BCRP: breast cancer resistance protein; CNT: concentrative nucleoside transporter; ENT: equilibrative nucleoside transporter; MATE: multidrug and toxin extrusion transporter; MRP: multidrug resistance protein; OAT: organic anion transporter; OCT: organic cation transporter; OCTN1: organic cation/ergothioneine transporter 1; OCTN2: organic cation/carnitine transporter 2; PEPT: peptide transporter; P-gp: p-glycoprotein; URAT: urate transporter.*

complex transmembrane transport mechanisms enable transcellular flow of substances both from the tubular lumen to the blood (reabsorption) and from the peritubular capillary to the tubular lumen and therefore to urine (tubular secretion). Cellular transmembrane transport takes place via proteins or protein complexes anchored in the cell membrane known as membrane transporters.

The process of tubular secretion comprises two steps: the first takes place at the basolateral pole of the proximal tubular cell via transporters at this site by extracting products to be eliminated from the blood circulating in the peritubular capillaries (or from the peritubular interstitial compartment) and internalizing and concentrating them in the cytoplasm of the proximal tubular cell; the second uses luminal membrane transporters to externalize and transfer these products from the cytoplasm towards the tubular lumen so that they can be eliminated in urine (Fig. 1). Several membrane proteins act as organic ion transporters in proximal tubular cells. These molecules are found in the basolateral cell membrane, in the luminal membrane, or in some cases they can be identified at both poles of the cell (Fig. 2). They manage a large amount of different organic ions, including drugs, whose pharmacokinetics, pharmacodynamics, and toxicity profile are closely dependent on them, as well as intermediary or residual metabolic products, hormones, and diverse environmental toxins. The participation of these transporters, as well as their expression and functionality, may vary from person to person and it is crucial for appropriate homeostasis and for preventing toxicity of organic anions and cations.

In vivo, the degree of interaction between a substrate and its membrane transporter are determined by the substrate concentration and its affinity for membrane transporter and the degree of competition with other substrates that use the same membrane transporter. In the case of drugs, some pharmacological interactions are due to competition for tubular secretion at this level[1]. Other determinants of the affinity of a transporter for a specific substrate are the structural variants of the protein itself or the protein group, which result from mutations or polymorphisms in the gene encoding the protein(s)[16].

Tubular transport of a specific organic ion can be disturbed as a result of alterations of either internalization to the tubular cell from the bloodstream or externalization from the cytoplasm to the tubular lumen. When the mechanism of transport altered is the internalization, it can accumulate in the blood, leading to overexposure and systemic side effects. However, if the mechanism of transport altered is the externalization, the ion accumulates inside the proximal tubular cell, thus potentially giving rise to tubular dysfunction.

Membrane transporters are usually multispecific or polyspecific. The same transporter can carry multiple substrates and the same substrate can be carried by several transporters, with greater or lesser affinity for each of them. Consequently, various substrates may compete for the same transporter, depending on the concentration of each substrate and their intrinsic affinity for each transporter. In addition, when a transporter is blocked, the substrate can be excreted –albeit less efficiently– by a different transporter.

Main families of renal tubular membrane drug transporters

The main proximal tubular cell organic ion membrane transporters are depicted in figure 2. They belong to two superfamilies: the solute carrier (SLC) transport protein family, which are indirectly associated with cellular energy and use the difference in transmembrane potential or concentration gradients as transport force, and the ATP-binding cassette (ABC) family, which uses the energy generated by ATP to function[1].

Organic cation transporters

Organic cation transporters (OCT) belong to the SLC superfamily, and are encoded by genes of the *SLC22A* family. The main OCT expressed in the kidney is OCT2 (SLC22A2), which is specific to this site, unlike OCT1 that is preferentially expressed in the liver[17] . OCT2 is expressed in the basolateral membrane of the proximal tubular cell and shows affinity for several endogenous substances, such as monoamine transmitters or creatinine, as well as for various cationic drugs[3,4]. Protein expression of human OCTs is affected by several genetic variants[18,19].

Organic cation/ergothioneine transporter 1 and organic cation/carnitine transporter 2

Organic cation/ergothioneine transporter 1 (OCTN1; SLC22A4) and organic cation/carnitine transporter 2 (OCTN2; SLC22A5) are expressed in the luminal membrane and participate in the transport of several drugs.

Multidrug and toxin extrusion transporters

Multidrug and toxin extrusion (MATE) transporters belong to the SLC47 family. The two main MATEs identified to date are MATE1 (SLC47A1) and MATE2-K (SLC47A2), both of which are preferentially expressed in the human kidney and found in the luminal membrane of the proximal tubular cell as proton gradient-dependent organic cation extrusion transporters[20]. The organic substrates secreted include creatinine[21]. In the epithelium of the renal proximal tubule, MATE1 cooperates with OCT2 expressed in the basolateral membrane for the renal secretion of various cations[20].

Organic anion transporters

Organic anion transporters (OAT) belong to the SLC superfamily and are characterized by their ability to accept several different endogenous and exogenous organic anions[22,23]. The main OATs present in the proximal renal tubule are OAT1, OAT2, OAT3, OAT4, OAT10, and the urate transporter URAT1. Both OAT1 and OAT3 are found in the basolateral membrane of the proximal tubular cell and exchange the extracellular anion for α-ketoglutarate, whereas OAT4 is found in the apical membrane. In addition to the extrusive function of the transported substrate, it can reabsorb various substances, including urate, by exchanging them for hydrogen ions or decarboxylate. However, the main urate transporter is URAT1, which is responsible for its reabsorption in exchange with monocarboxylate at the proximal tubular level and the target of uricosuric drugs. OAT10 is also found in the luminal membrane and transports nicotinate and several drugs[22,23].

Nucleoside transporters: concentrative nucleoside transporters and equilibrative nucleoside transporters

Concentrative nucleoside transporters (CNT; SCL28) and equilibrative nucleoside transporters (ENT; SCL29) are responsible for the transport of nucleosides and nucleoside analogs, most of which are used as antiviral and anticancer drugs[24,25]. Transporters CNT1, CNT2, and CNT3, together with ENT4, are expressed in the luminal membrane, whereas ENT1 and ENT2 are expressed mainly in the basolateral membrane. As a group, they reabsorb nucleosides from the tubular lumen toward the bloodstream. Transporter ENT1 is also expressed in the luminal membrane where it has a secretory function[24,25].

Peptide transporters

Peptide transporters PEPT1 (SLC15A1) and PEPT2 (SLC15A2) are expressed in the luminal membrane of the cell and reabsorb various dipeptides and tripeptides, and some peptidomimetic substrates[26].

P-glycoproteins

In the kidney, P-glycoproteins (P-gp) (ABCB1) are expressed in the luminal membrane of the proximal tubular cell with a wide range of substrates based on different chemical structures[27].

Multidrug resistance proteins

Multidrug resistance proteins (MRP) belong to the ABC superfamily. The main MRPs expressed in the proximal renal tubule are MRP2 (ABCC2) and MRP4 (ABCC4) (both in the luminal membrane of the cell) and mediate secretion of various anionic drugs. MRP6 (ABCC6), which is preferentially expressed in the basolateral membrane, seems to have a specificity limited to a few glutathione conjugates[28].

Breast cancer resistance protein

Breast cancer resistance proteins (BCRP) belong to the ABC superfamily. They are expressed in the luminal membrane of the proximal tubular cell and accept various organic ions and drugs. Urate has also been described as a substrate. The BCRPs share some substrates with P-gp and MRP2 as a complementary effect in the efflux mechanism of the substrates from the cell to the tubular lumen[29].

Renal tubular membrane transporters and antiretroviral drugs

Nucleoside reverse transcriptase inhibitors

Zidovudine (AZT) and lamivudine (3TC) are eliminated by the kidneys through active tubular secretion and glomerular filtration. Transport in the kidneys involves OATs, OCTs, and nucleoside transporters[30,31]. Between 15 and 20% of AZT is excreted unchanged via the kidneys, although 60-70% of the drug recovered in urine takes the form of an inactive glucuronide metabolite. Renal transport of AZT is mediated mostly by the OAT system in the basolateral membrane and by the OCTs in the apical membrane[30,31]. Cimetidine, an OCT inhibitor, and probenecid, a standard OAT inhibitor, inhibit renal excretion of AZT[31]. Between 70 and 80% of 3TC is secreted unchanged in urine; the fact that its clearance exceeds its glomerular filtration implies active tubular secretion, which is mediated by the OCT system. In addition, it is believed to be a substrate of MRP4[30,31].

Didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) are eliminated mainly through glomerular filtration, although tubular secretion contributes to their excretion. Didanosine is also a substrate of OATs, and when used in combination with TDF may boost toxicity of TDF[32-34]. There is inconclusive evidence that abacavir, emtricitabine (FTC), and d4T interact with OATs and OCTs[33,35,36].

Tenofovir, along with cidofovir, adefovir, acyclovir, and ganciclovir are diphosphorylated analogs of acyclic nucleosides. They are all actively secreted in the kidney and are substrates of OAT1 and MRP2. Tenofovir is transported by OAT1 and OAT3 in the basolateral membrane of the proximal tubular cell[37]. Tenofovir shows 20-fold greater affinity for OAT1 than for OAT3, although expression of OAT3 in the proximal tubule is greater than that of OAT1[5]. Efflux of tenofovir from the tubular cell is essentially mediated by MRP4[37,38]. Both transporters (OAT1 and MRP4) act coordinately to the renal elimination of tenofovir[5,37].

Nonnucleoside reverse transcriptase inhibitors

No renal transport systems have been identified for nevirapine or efavirenz. Etravirine is not a substrate of

transporters from the ABC superfamily, although it is a potent BCRP inhibitor and induces numerous transporters from the ABC superfamily, especially BCRP[14]. Rilpivirine inhibits P-gp, OCT1, and OCT2; therefore, it can interact with their substrates[6].

Protease inhibitors

Protease inhibitors are metabolized primarily in the liver. Renal clearance is minimal (< 1%) for amprenavir and fosamprenavir, 1.2% for darunavir, 1-5% for ritonavir, 1-3% for saquinavir, 7% for atazanavir, and 10% for indinavir. These drugs carry a positive charge and can interact with OATs[2,15,39]. Some of them, in particular ritonavir, can inhibit several transporters in renal tubular cells, including OAT1, OAT2, MRP2, MRP4 and MATE1[8,9,30,40,41]. The PIs can also act as substrates and inhibitors of P-gp, especially ritonavir[7,30,40].

Integrase inhibitors

In vitro, raltegravir is a substrate that weakly inhibits OAT1, OAT3, OCT2, BCRP, MATE1, and MATE2-K[42]. Dolutegravir inhibits OCT2 *in vitro* and *in vivo*[13,43,44].

Cobicistat

Cobicistat is a potent cytochrome P450 3A (CYP 3A) inhibitor and acts as a potent pharmacokinetic booster[45]. It is also an inhibitor of OCT2 and MATE2-K, and an even more potent inhibitor of MATE1[7].

Renal tubular membrane transporters and tubular secretion of creatinine

Creatinine is a weak organic cation that is generated through creatine metabolism. Although it is eliminated mainly via glomerular filtration, in subjects with normal renal function, active tubular secretion accounts for 10-40% of creatinine clearance[46]. This amount can increase up to 50% in cases of chronic kidney disease, leading to overestimation of glomerular filtration[47]. The process of tubular secretion of creatinine has not been completely elucidated. It is known that it involves several membrane transporters, with OCT2 being the main transporter in the basolateral membrane of the proximal tubular cell[3,4]. It acts as a non-saturable transporter, even in situations of renal insufficiency, when plasma creatinine increases. It has recently been postulated that OATs can also participate in the secretion of creatinine[9,48,49]. *In vitro* investigations suggest that OAT2 in particular may make a substantial contribution to creatinine secretion, facilitating the most efficient transport of creatinine of any of the human creatinine transporters identified[4,9]. Once creatinine has been internalized into the tubular cell, its secretion to the tubular lumen is mediated by MATE transporters, mainly MATE1[9,21] (Fig. 3).

Clinical implications of renal transporter-mediated interactions of antiretroviral drugs

To understand the clinical implications of renal transporter-mediated interactions of antiretroviral drugs we will consider the following aspects: (i) drug-drug interactions whose molecular basis involves competition, inhibition, or induction of transporters; (ii) genetic modifications in transporters and intrinsic characteristics of the host which translate into functional effects, and (iii) interference in the transport of endobiotic products via drug transporters, with particular reference to creatinine transport. Finally, a set of recommendations for clinical use of antiretrovirals that interfere with renal transporters of creatinine will be proposed.

Drug-drug interactions at the level of renal transporters

Several potential interactions based on membrane transporters occur via competitive or inhibitory mechanisms[40] (Tables 1 and 2). The classic example of drug-drug interaction is seen between PIs and other HIV drugs. Although most are based on inhibition or induction of cytochrome P450, many of these drugs, such as ritonavir and lopinavir, are potent inhibitors of P-gp, and some can also induce their functional expression[40]. Protease inhibitors and NRTIs can also interact with OCTs; an *in vitro* interaction between abacavir and AZT with 3TC resulting from inhibition of OCT1 and OCT2 has been reported[50]. A similar phenomenon was demonstrated for emtricitabine owing to inhibition of OCT2[35,36]. Inhibition of OCTs by PIs and NRTIs may be relevant for the pharmacokinetics of metformin, which is a substrate of OCT1.

Drug-drug interactions at the level of renal transporters may result in an increased risk of drug toxicity. As mentioned above, ddI is a substrate of the OATs and potentiation of kidney toxicity between didanosine and TDF is well documented[34,51,52]. Several cohort studies have found a greater decrease in estimated glomerular filtration rate (eGFR) when TDF is used with a boosted

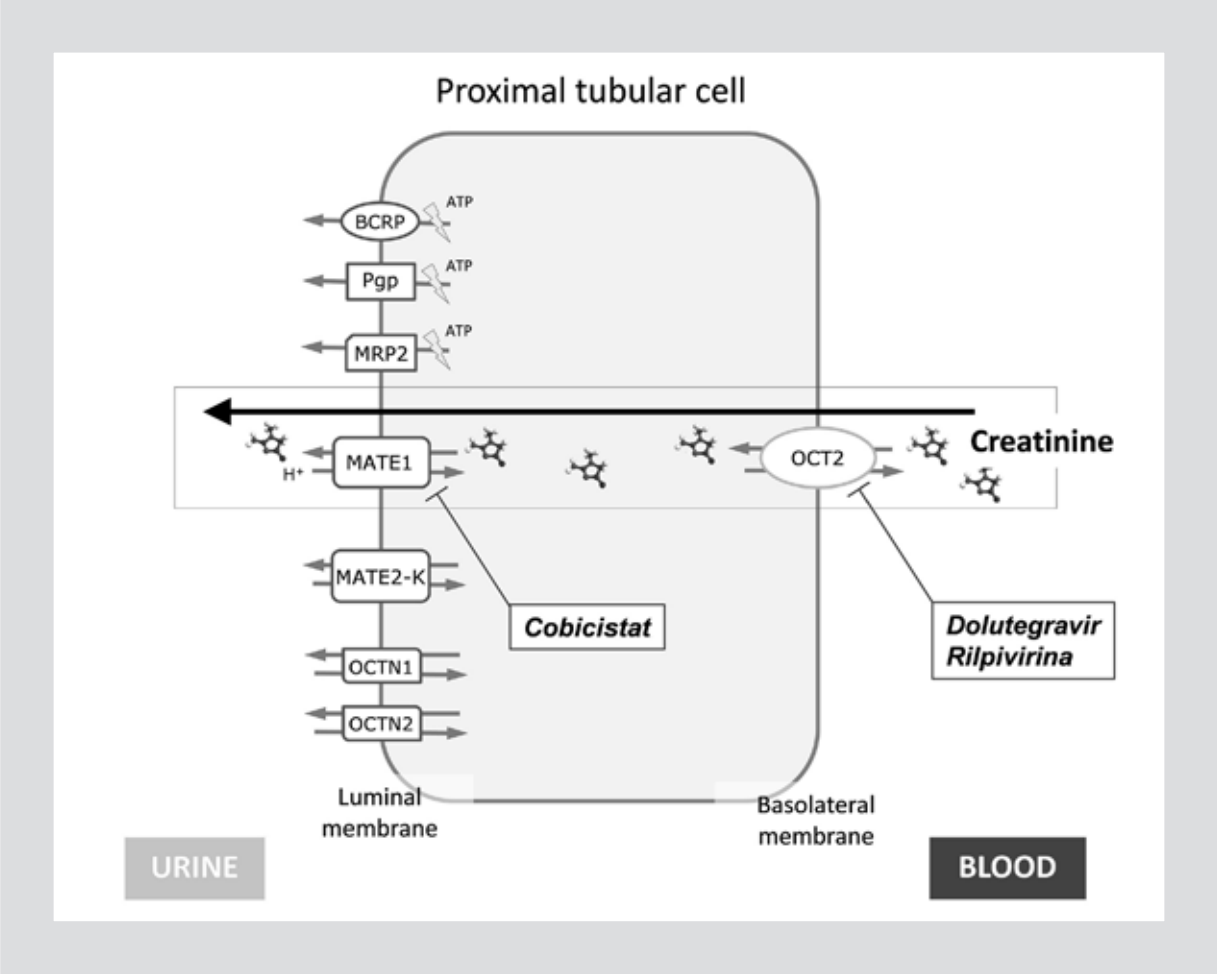

Figure 3. *Tubular secretion of creatinine and inhibitory effects of some antiretrovirals on membrane transporters. BCRP: breast cancer resistance protein; MATE: multidrug and toxin extrusion transporter; MRP: multidrug resistance protein; OCT: organic cation transporter; OCTN1: organic cation/ergothioneine transporter 1; OCTN2: organic cation/carnitine transporter 2.*

PI as compared with other antiretroviral drugs[32]. Clinical studies have also shown that ritonavir reduces tenofovir renal clearance in humans[53] and increased tenofovir plasma concentrations have been associated with the development of tubular toxicity[54]. Since ritonavir inhibits several transporters in renal tubular cells[8,9,30,40,41,55], an interaction at the level of transporters involved in efflux of tenofovir from the tubular cell has been considered the most likely mechanism. However, *in vitro* experiments suggest that ritonavir is a substrate for MRP2[56] and it has a minimal effect on MRP4, the main apical tubular transporter of tenofovir[41]. Therefore, the mechanism of increased tubular tenofovir exposure when used in combination with boosted PIs has not been fully elucidated and may result in part from the inhibitory effect of ritonavir on P-gp[57]. Although there are still insufficient data to determine if co-administration of TDF with COBI is associated with a greater risk of renal adverse reactions compared with regimens that include TDF without COBI, in a recent study under pharmacologically relevant conditions, COBI exhibited minimal interference with the functions of transport pathways currently known to be involved in the active renal tubular secretion of tenofovir[7].

The renal elimination of antiretrovirals or other drugs used in HIV-infected patients may be subject to other renal drug-drug interactions that may modify the risk of kidney injury. An interaction between TDF and non-steroidal anti-inflammatory drugs at the level of MRP4 may entail a risk of accumulation of tenofovir in tubular cells, thus favoring kidney injury[58]. Trimethoprim and probenecid are competitive inhibitors of other drugs. When administered with AZT, they increase its area

Table 1. Interactions of nucleoside/nucleotide and nonnucleoside reverse transcriptase inhibitors with renal drug transporters*

	ABC Superfamily		SLC Superfamily	
	Substrate	**Inhibitor**	**Substrate**	**Inhibitor**
Nucleoside/nucleotide reverse transcriptase inhibitors				
Zidovudine	MRP4, BCRP	BCRP	OAT 1-4, CNT1, CNT3, ENT2	CNT1
Didanosine	BCRP	P-gp	CNT2, CNT3, ENT1, ENT2	OAT1, OAT3
Stavudine	BCRP, MRP5	P-gp	CNT1	OAT1, OAT3, CNT1
Lamivudine	BCRP	P-gp, MRP1	OCT1, OCT2, CNT1	OCT1-3, CNT1
Emtricitabine	MRP1	P-gp, MRP1		
Tenofovir	P-gp, BCRP, MRP4	P-gp, MRP1-3	OAT1, OAT3	
Nonnucleoside reverse transcriptase inhibitors				
Efavirenz		P-gp, BCRP, MRP1-3		
Nevirapine		P-gp, MRP1-3		
Etravirine		P-gp		
Rilpivirine		P-gp		OCT1, OCT2, OCT3

*Organic anion transporting polypeptides, which have a scarce presence in the kidney, are not listed in the table.
ABC: ATP-binding cassette family; SLC: solute carrier transport protein family; MRP: multidrug resistance proteins; BCRP: breast cancer resistance protein; OAT: organic anion transporters; CNT: concentrative nucleoside transporters; ENT: equilibrative nucleoside transporters; P-gp: p-glycoproteins; OCT: organic cation transporters.

under the curve from 80 to 115%[40]. Probenecid also increases concentrations of acyclovir, and trimethoprim increases those of 3TC, although the differences do not appear to be clinically relevant[40]. Probenecid inhibits the renal secretion of anionic drugs that occurs via OATs and blocks tubular secretion of ganciclovir[40]. Thanks to its ability to inhibit OAT1, probenecid is used in clinical practice to prevent the nephrotoxicity induced by cidofovir, an antiviral agent that accumulates in tubular cells via OAT1, resulting in cytotoxicity[59].

Genetic variants and characteristics intrinsic to the host

As mentioned above, TDF is transported to renal tubular cells by OATs encoded by *SLC22A* genes and is excreted in urine by MRPs, especially MRP4, which are encoded by *ABCC* genes[38]. A number of genetic studies have found that polymorphisms in *ABCC* genes are associated with plasma/intracellular concentrations and/or renal clearance of tenofovir and/or tubular dysfunction associated with this drug, whereas polymorphisms in *SLC22A* are not[10,11,60-62]. The polymorphism 669C>T in *ABCC4,* which encodes MRP4, has been associated with renal tubular damage[62]. Although the role of MRP2 in tenofovir transport remains unclear, polymorphisms in *ABCC2* (the gene encoding MRP2) have also been linked with tenofovir-associated tubular dysfunction[61,62]. Finally, a recent study has identified an association between a polymorphism in *ABCC10,* which encodes MRP7, with the onset of phosphaturia and β2-microglobinuria in patients treated with tenofovir[63].

P-glycoproteins, which are encoded by the gene *ABCB1 (MDR1),* have been thoroughly investigated. The single-nucleotide polymorphism 3435 C>T in this gene, which is associated with expression of P-gp, has been related with lower plasma concentrations of efavirenz[64] and a lower risk of liver toxicity in patients treated with nevirapine[65]. Polymorphisms at *MDR1* significantly influence atazanavir plasma concentrations[66]. Transcription of metabolic enzymes and transporter proteins is regulated by nuclear factors, the most important of which is the pregnane X receptor, encoded by the *NR1I2* gene. Pregnane X receptor regulates

Table 2. Interactions of protease inhibitors, integrase inhibitors, maraviroc, and cobicistat with renal drug transporters*

	ABC Superfamily		SLC Superfamily	
	Substrate	**Inhibitor**	**Substrate**	**Inhibitor**
Protease inhibitors				
Atazanavir	P-gp, MRP1, MRP2	P-gp, MRP1, BCRP		OCT1, OCT2
Ritonavir	P-gp, MRP1, MRP2	P-gp, MRP1, BCRP		
Fosamprenavir		BCRP		
Amprenavir	P-gp	P-gp, BCRP		
Lopinavir	P-gp, MRP1, MRP2	P-gp, BCRP		
Saquinavir	P-gp, MRP1, MRP2	P-gp, MRP1, BCRP		OCT1, OCT2
Darunavir	P-gp	P-gp		
Indinavir	P-gp, MRP1, MRP2	MRP1		OCT1, OCT2
Tipranavir	P-gp	P-gp		
Nelfinavir	P-gp	P-gp, BCRP		OCT1, OCT2
Integrase inhibitors				
Raltegravir	P-gp			
Dolutegravir	P-gp			OCT2
Maraviroc	P-gp	P-gp		
Cobicistat				OAT3, OCT2, MATE K-2 (weak), MATE-1

*Organic anion transporting polypeptides, which have a scarce presence in the kidney are not listed in the table.
ABC: ATP-binding cassette family; SLC: solute carrier transport protein family; MRP: multidrug resistance proteins; BCRP: breast cancer resistance protein; OAT: organic anion transporters; CNT: concentrative nucleoside transporters; ENT: equilibrative nucleoside transporters; P-gp: p-glycoproteins; OCT: organic cation transporters; MATE: multidrug and toxin extrusion transporters.

expression of CYP3A4, ABCB1 (P-gp), and SLCO1B1 (OATP1B1). The polymorphism *NR1I2* –63396C has been associated with variations in exposure to atazanavir[67].

Lopinavir is a substrate for the efflux transporters Pgp, MRP1, and MRP2, which are encoded, respectively, by *ABCB1, ABCC2,* and *ABCC2.* The polymorphism 4544G>A in *ABCC2* has been associated with intracellular accumulation of lopinavir[68]. The polymorphism *MRP2* 24 C>T has been associated with a 24% greater clearance of indinavir[69]. The concentration of raltegravir is affected by the polymorphism *ABCB1* –3435C>T, and patients with the CT or TT genotype have lower concentrations than those who harbor the CC genotype[63].

It is widely reported that aging is associated with a decline in glomerular filtration, although organic anion transport also declines with age[70] in contrast with renal cationic drug secretion[71].

Inflammation leads to downregulation of OAT1 and OAT3 and can modify renal secretion and produce systemic accumulation of anionic drugs[72]. Expression of nucleoside transporters is also affected by inflammatory status, and inflammatory cytokines have been shown to induce their expression[73].

Interference with creatinine transport

As mentioned above, several commonly used drugs from different therapeutic classes interfere with renal active tubular secretion of creatinine and thus may lead to a spurious increase in its serum concentrations[12,13,74-86] (Table 3). These include trimethoprim, pyrimethamine, dronedarone, and the H2 receptor blocker cimetidine[74,77,78,87]. The most remarkable effects, with increases in plasma creatinine levels between 0.24 and 0.37 mg/dl and decreases in creatinine clearance of 15-34 ml/min per 1.73 m^2, have been

Table 3. Effects of drugs that interfere with renal active tubular secretion of creatinine on serum creatinine concentrations and creatinine clearance

	Change in serum creatinine concentrations (mg/dl)	Change in creatinine clearance (ml/min/1.73 m^2)
Antiretroviral drugs		
Rilpivirine	↑0.10[79,85,86]	↓5-11[79,85,86]
Dolutegravir	↑0.10-0.15[13]	↓10-14[13]
Cobicistat	↑0.11-0.18[12,84]	↓10-15[12,84]
Drugs other than antiretrovirals		
Cimetidine	↑0.37[74]	↓15[74]
Trimethoprim	↑0.28[77]	↓16[77]
Pyrimethamine	↑0.24[78]	↓34[78]
Amiodarone	↑~0.11[80]	Not reported
Dronedarone	Not reported	↓19[81]

reported with cimetidine[74], trimethoprim[77] and pyrimethamine[78] (Table 3). The rises in creatinine levels with these drugs are due to inhibition of the renal active tubular secretion of creatinine[88]. Although all drugs known to affect creatinine seem to inhibit OCT2 and MATE1 to some extent[9], they may have predominant effects on certain transporters. Pyrimethamine is a potent and selective inhibitor of MATE1 and MATE2-K[89], causing substantial increases in serum creatinine levels[78]. Trimethoprim is a relatively potent inhibitor of MATE2-K and cimetidine most potently inhibits MATE1, although it has inhibitory effects on all creatinine transporters[9].

As for antiretroviral drugs, interactions with the transport of creatinine have been identified with RPV[6], DTG[13] and the pharmacoenhancer COBI[7,9,12]. While RPV and DTG inhibit mainly the renal transporter OCT2[6,13], COBI, similarly to cimetidine, predominantly inhibits MATE1 with a weaker effect on the other transporters[7,9] (Fig. 3).

The interaction of antiretroviral drugs with the transporters involved in tubular secretion of creatinine can cause mild-to-moderate increases in serum creatinine concentrations and moderate reductions in eGFR that do not translate into decreases in real glomerular filtration[90]. The absence of effect of these non-progressive increases in serum creatinine levels on actual renal function has been well documented in two recent studies on healthy volunteers exposed to DTG[13] and COBI[12] by comparing creatinine clearance with actual GFR using iohexol, a probe drug excreted by glomerular filtration. In a placebo-controlled study with DTG in healthy subjects, Koteff, et al.[13] showed that administration of this drug decreased serum creatinine clearance by 10-14%, but had no effect on measured glomerular filtration rate (by plasma clearance of iohexol) or renal plasma flow. Likewise, the administration of COBI in subjects with normal renal function (creatinine clearance > 80 ml/min) resulted in reduced eGFR with minimal change in the actual GFR measured by plasma clearance of iohexol (–9.9 vs. –2.7 ml/min)[12]. Similar results (–11.9 vs. –3.6 ml/min) were observed in the same study in those individuals with mild/moderate renal impairment (creatinine clearance 50-79 ml/min)[12].

Recommendations for clinical use of antiretroviral drugs that interfere with tubular secretion of creatinine

The main challenge that clinicians face when using drugs that inhibit active tubular secretion of creatinine is to reliably distinguish between benign, non-significant increases in serum levels and real kidney damage. Creatinine increases due to inhibition of tubular secretion have two characteristics: they appear early after initiation of therapy and are predictable. As stated above, when antiretroviral agents that interfere with tubular secretion of creatinine (i.e. RPV, DTG, COBI) are administered, it is reasonable to expect a slight increase in serum creatinine level and, consequently,

Table 4. Key features of changes in serum creatinine concentrations and estimated glomerular filtration rate when using HIV drugs (i.e. rilpivirine, dolutegravir, cobicistat) that interfere with tubular secretion of creatinine

- Changes occurring shortly after the initiation therapy with the HIV drug, usually within the first days or weeks.
- Slight and predictable increase in serum creatinine concentrations (≤ 0.2 mg/dl) and decrease in eGFR (≤ 15 ml/min).
- Serum urea concentrations unaltered.
- Absence of proteinuria, hematuria, or normoglycemic glucosuria.
- Non-progressive changes after 4 weeks.

eGFR: estimated glomerular filtration rate.

Table 5. Key findings indicating renal tubular damage in patients receiving tenofovir disoproxil fumarate in combination with drugs that interfere with tubular secretion of creatinine

- Marked or progressive increase in serum creatinine concentrations (> 0.2 mg/dl from baseline) or eGFR decline (> 15 ml/min) from baseline.
- Hypophosphatemia with increased fractional excretion of phosphate (> 20%).
- Hypouricemia with increased fractional excretion of urate (> 20%).
- Normoglycemic glycosuria.
- Tubular proteinuria (urine albumin/total protein < 0.4).

eGFR: estimated glomerular filtration rate.

a decrease in the eGFR using equations that include serum creatinine concentration or by calculation of creatinine clearance in 24-hour urine (Table 3), without causing a true effect on real glomerular filtration. Since creatinine is widely used in clinical practice as a marker of renal function, this can give cause for concern, especially when the patient is receiving antiretroviral combinations that include other HIV drugs with nephrotoxic potential such as TDF or atazanavir. Renal toxicity leading to discontinuation of TDF occurred in about 1% of patients receiving TDF in combination with COBI in recent clinical trials[91,92]. Therefore, care providers should pay attention to this complication. Food and Drugs Administration and European Medicines Agency (EMA) state that the combination of TDF and COBI should not be initiated in patients with eGFR < 70 ml/min[93,94]. The EMA Summary of Product Characteristics of Stribild®, a single-tablet regimen consisting of TDF, emtricitabine, elvitegravir, and COBI, recommends not to initiate this combination in patients with eGFR < 90 ml/min, unless this regimen is considered the preferential treatment for the individual patient[94]. To safely use these combinations, clinicians must correctly interpret changes in serum creatinine upon initiation of therapy (Table 4), and differentiate the mild-to-moderate elevations in serum levels of this marker from clinically significant toxicity (Table 5). This can usually be accomplished by adhering to current clinical practice guidelines on renal monitoring of patients receiving TDF[55,95-99], that is, regular check-ups, including determination of serum creatinine and eGFR, serum phosphate and uric acid, urinalysis and measurement of proteinuria using the protein:creatinine ratio to rule out tubular damage. In the particular case of Stribild®, the EMA recommends check-ups every four weeks during the first year, and then every three months[94].

As discussed above and shown in table 4, changes in serum creatinine concentrations caused by pharmacologic interference in tubular transport are observed within the first weeks after initiation of treatment[85,86,91,92,100-102]. Therefore, renal function should be assessed approximately 4-8 weeks after therapy is initiated to determine the new eGFR to be used as reference for monitoring. Mild-to-moderate, non-progressive declines in eGFR of up to 15 ml/min are anticipated and should not raise concerns of renal toxicity unless they are accompanied by other markers of renal damage (Table 5). The main findings indicating renal damage are marked or progressive increase in creatinine or decline in eGFR, hypophosphatemia or hypouricemia, and urine abnormalities (normoglycemic glycosuria or proteinuria). The work-up should be extended in such cases with more specific tests, including measurement of fractional phosphate excretion, and urate excretion, urine albumin-to-protein ratio, urine and serum potassium, and acid-base balance in the blood.

In figure 4 we outline preliminary authors' opinion-based recommendations for monitoring renal function in this context, which should be revised according to the availability of evidence-based data.

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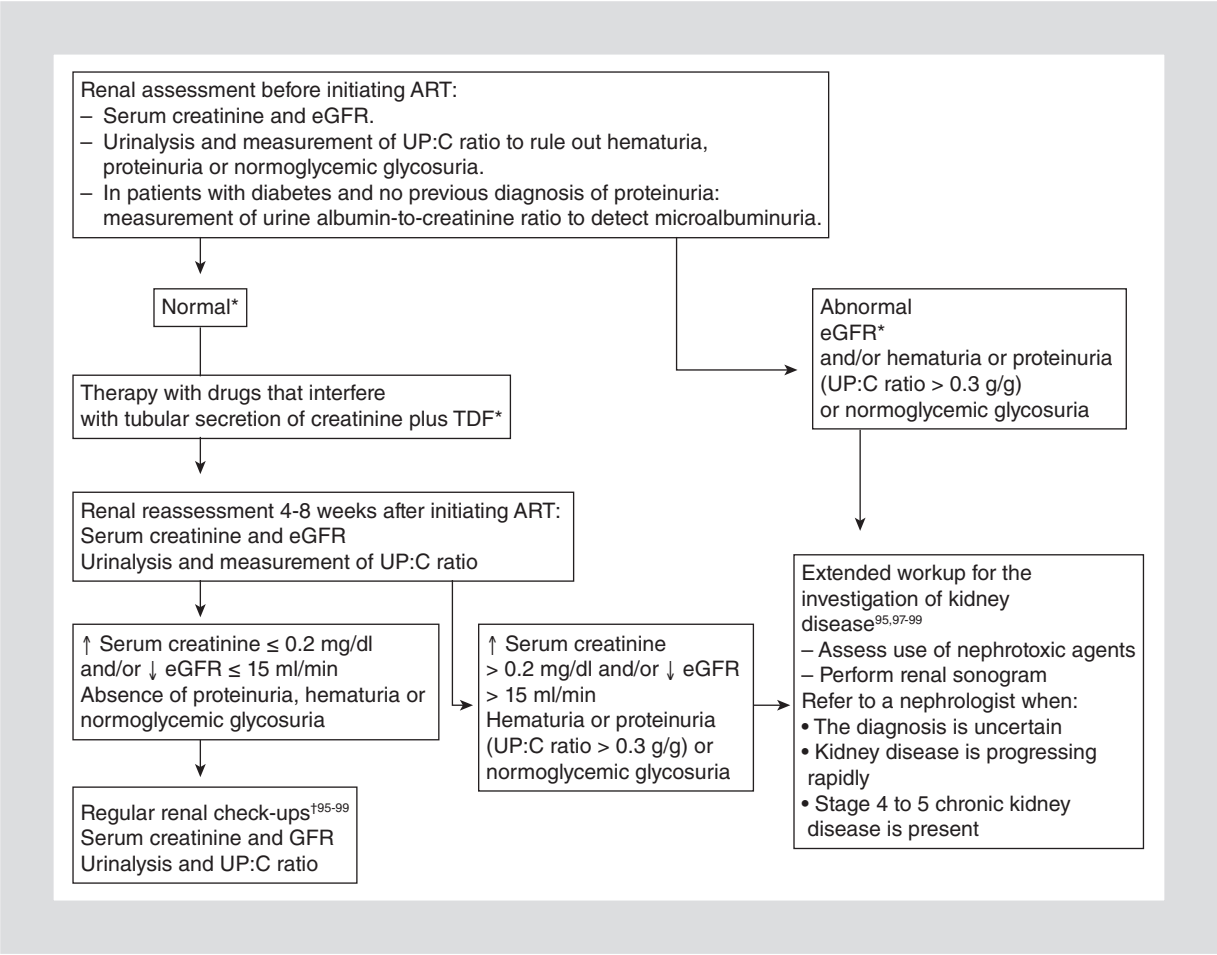

Figure 4. *Proposal for the monitoring of renal function in clinical practice when using antiretrovirals that interfere with tubular secretion of creatinine.*

**Food and Drug Administration and European Medicines Agency (EMA) state that the combination of TDF and cobicistat should not be initiated in patients with creatinine clearance < 70 ml/min[93,94]. The EMA summary of product characteristics of Stribild®, a single-tablet regimen consisting of TDF, emtricitabine, elvitegravir and cobicistat, recommends not initiating this combination in patients with creatinine clearance < 90 ml/min unless this regimen is considered the preferential treatment for the individual patient[94].*

†The EMA summary of product characteristics states that renal assessments should be repeated every four weeks during the first year and then every three months during Stribild® therapy[94].

ART: antiretroviral therapy; TDF: tenofovir disoproxil fumarate; eGFR: estimated glomerular filtration rate; UP:C: urine protein to creatinine ratio.

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