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HIV and HCV Medications in End Stage Renal Disease

Keiko I. Greenberg¹, Mark A. Perazella², and Mohamed G. Atta¹

¹The Johns Hopkins University School of Medicine, Department of Medicine

²Section of Nephrology, Department of Medicine, Yale University School of Medicine

Abstract

Human immunodeficiency virus (HIV) infection and hepatitis C virus (HCV) infection affect populations worldwide. With the availability of over 35 Food and Drug Administration approved medications for treatment of HIV, the morbidity and mortality associated with HIV has greatly improved. On the other hand, treatment options for HCV have been limited until very recently. While the use of protease inhibitors (such as boceprevir and telaprevir) has become standard of care for treatment of hepatitis C in the general population, data for individuals with impaired kidney function, particularly those on dialysis, are extremely limited. Use of medications in dialysis patients can be challenging given the dose adjustments that must be made for renally cleared molecules, and potentially increased impact of adverse effects such as anemia. Recommendations for dosing of marketed therapies for HIV and HCV are reviewed.

Globally, an estimated 35 million individuals are living with human immunodeficiency virus (HIV) (1). Although the number of new HIV cases and acquired immunodeficiency syndrome (AIDS)-related deaths is decreasing, the prevalence of the disease is increasing due to the reductions in HIV morbidity and mortality seen with combined antiretroviral therapy (cART) (2). With the availability of cART, individuals with HIV are able to control HIV replication for many years and delay or avoid progression to AIDS. As individuals with HIV have been living longer, they are developing the same chronic diseases that affect individuals without HIV. This includes chronic kidney disease (CKD) and its associated complications. Causes of CKD in the HIV patient include HIV-associated nephropathy, HIV-associated immune complex kidney disease, drug-related nephrotoxicity, diabetes mellitus, and arteriosclerosis, to name a few (3). As a result, HIV infection in the dialysis population has become more common. The prevalence of HIV infection among end-stage renal disease (ESRD) patients has been estimated to be approximately 1.5% (4), although this may be an underestimate of current rates (5) as more recent estimates are not available.

Hepatitis C virus (HCV) infection affects 80-170 million individuals worldwide (6, 7). Without treatment, HCV can lead to cirrhosis, liver failure, hepatocellular carcinoma, and kidney disease (membranoproliferative glomerulonephritis with or without cryoglobulinemia). Therapeutic options for HCV have been limited until recently. With the development of direct-acting antiviral agents, the standard of care for treatment of HCV has

changed. Several additional drugs are in development, the success of which may ultimately lead to treatment regimens free of interferon and ribavirin (8).

Unlike HIV infection, relatively few patients, particularly those with impaired kidney function, are treated for hepatitis C. In the Dialysis Outcomes and Practice Patterns Study, the prevalence of HCV was nearly 10%, but only 1% of the HCV positive patients were prescribed antiviral medications (9). This is likely due to side effects of available therapies and limited efficacy. There is a significant need for more effective and better tolerated therapies in the HCV infected dialysis population, who face increased mortality compared to other populations with ESRD (10).

A subset of this group that is at particularly high risk of morbidity and mortality are those who are co-infected with both HIV and HCV. In the United States, between 2-30% of HIV-positive individuals have been estimated to be co-infected with HCV (11). These individuals appear to be at higher risk of developing AIDS, cirrhosis/liver failure, and death (11). Here, dosing recommendations of available therapies for HIV and HCV infections are presented.

Dosing of HIV Medications in Dialysis

Most patients with HIV are treated with a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a drug from another class. Dosing of anti-retrovirals can be challenging as drug interactions are common. In addition, most NRTIs are cleared by the kidneys. Mechanisms of renal elimination of these drugs include glomerular filtration and tubular secretion of drugs. Several organic cation and anion transporters have been identified to have a role in their excretion in the proximal tubule (12-14).

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs prevent incorporation of viral RNA into host DNA by inhibiting HIV reverse transcriptase (15). Zidovudine was the first NRTI and the first antiretroviral drug approved by the FDA in 1987. With the exception of abacavir, which is metabolized by alcohol dehydrogenase and glucuronyl transferase and does not need dose adjustment with impaired renal function, the NRTIs require dose adjustment for dialysis patients (15). Tenofovir is one of the most commonly used NRTIs. Tenofovir is excreted by glomerular filtration and by tubular secretion, which occurs through organic anion transporter (OAT) 1 and OAT3 on the basolateral membrane and multidrug-resistance protein (MRP) 4 and MRP7 on the apical membrane (16, 17). Tenofovir increases didanosine levels (16, 18) and the risk of didanosine related toxicity; therefore the co-administration of these two drugs is not recommended (19). The other NRTIs are also primarily excreted by the kidneys and require dosage adjustment in dialysis patients as indicated in **Table 1**.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs are noncompetitive inhibitors of HIV reverse transcriptase (15). Nevirapine was the first of this class to be approved by the FDA in 1996 (15). All members of this class are metabolized by cytochrome P450 3A4 (CYP3A4), and renal excretion appears to be minimal at approximately 5% or less depending on the drug (20-24). Therefore, dose adjustments for renal impairment have not been recommended, although caution is urged

due to the lack of available data on these drugs in hemodialysis patients and in those with impaired kidney function. Delaviridine, efavirenz, etravirine, and nevirapine all induce CYP3A4 raising the possibility of significant drug interactions with other CYP3A4 substrates, inducers or inhibitors (15). Although rilpivirine is known to interact with several enzymes involved in drug metabolism, including P-glycoprotein, organic cation transporter 2 (OCT2), organic anion transporter peptide 1B1 (OATP1B1) and CYP3A4, the likelihood of drug interactions is thought to be minimal due to low plasma drug concentrations (16).

Protease inhibitors

Protease inhibitors prevent formation of mature virus by blocking HIV protease (15). The first of these, saquinavir, was approved by the FDA in 1995. These agents are primarily metabolized by the liver through CYP3A4. Urinary excretion accounts for less than 10% (25). Available data suggest that clearance by dialysis is minimal. Thus, no dosage adjustments are recommended in individuals with impaired renal function (26). However, protease inhibitors interact with many other drugs, including the direct-acting antiviral agents for HCV (see below), due to inhibition of CYP3A4.

Integrase strand transfer inhibitors

Integrase inhibitors prevent the incorporation of HIV DNA into host DNA by blocking the integrase enzyme (15). Raltegravir was the first drug of this class to be approved by the FDA in 2007. It is primarily metabolized by UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1) and partly by CYP3A4. Although it has been reported that 30% of raltegravir is excreted into the urine (15), no clinically significant pharmacokinetic differences have been observed in individuals with underlying kidney disease compared to normal renal function, and no dose adjustment is recommended (27). Clearance of raltegravir by hemodialysis was minimal in 2 dialysis patients (28).

Dolutegravir is metabolized by glucuronidation and urinary excretion is negligible (16). A higher dosage of dolutegravir is recommended when used with drugs that induce UGT1A1 and CYP3A4, notably efavirenz, boosted fosamprenavir, and tipranavir. Dolutegravir inhibits OCT2, which has several commonly used substrates such as metformin; this inhibition also mediates decreased tubular secretion of creatinine and raises serum creatinine in individuals with at least some degree of kidney dysfunction (16). In one pharmacokinetic study, dolutegravir pharmacokinetics differed slightly between individuals with creatinine clearance (CrCl) <30 ml/min compared to those with normal renal function; however, this difference was not thought to be clinically significant (29). No dosage adjustment is endorsed in severe renal impairment, although dolutegravir has not been studied in dialysis patients (30). Since dolutegravir is highly bound to plasma proteins, it is unlikely that the drug is cleared significantly by dialysis (30). Recently, a fixed-dose combination containing dolutegravir and the NRTIs abacavir and lamivudine was FDA approved for use in HIV positive patients. This fixed combination is not recommended in patients with CrCl <50 ml/min and is not appropriate for use in the dialysis population.

Elvitegravir is only available in a fixed dose combination pill that also contains cobicistat, emtricitabine, and tenofovir (15). Given the dose adjustments required of some of these

components in renal impairment, this combination is not recommended in patients with CrCl <70 ml/min or in those on dialysis.

CCR5 antagonist

Maraviroc prevents HIV from entering the CD4 cell by binding to the CCR5 receptor (15). The drug was approved by the FDA in 2007 for use only in patients with the CCR5-tropic virus. Approximately 25% of the drug is cleared by the kidneys (19). Maraviroc pharmacokinetics in individuals with varying degrees of renal impairment demonstrated that drug levels were similar between subjects with normal kidney function and those on hemodialysis (31). Dialysis did not affect drug levels. However, due to very high drug levels observed when maraviroc was co-administered with saquinavir/ritonavir in individuals with mild to moderate renal impairment, use of maraviroc with CYP3A4 inducers or inhibitors is not recommended in individuals with any level of renal impairment (31, 32).

Fusion inhibitor

Enfuvirtide inhibits fusion of the HIV virus to CD4 cells by binding to the envelope glycoprotein gp41 (15). It is a peptide that was approved by the FDA in 2003 for patients with viral replication despite treatment with cART. Metabolism of enfuvirtide is assumed to occur through its degradation into amino acids (33). A pharmacokinetic study of enfuvirtide in subjects with normal kidney function, CKD and ESRD showed no clinically significant difference in drug exposure in hemodialysis patients compared to those with normal kidney function (34). Since dialysis does not remove a significant amount of the drug, no dosage adjustment is recommended in ESRD patients (33).

Fixed Dose Combination Pills

Several combination pills have been marketed to decrease pill burden for patients with HIV. However, as many of these contain NRTIs which require dose adjustment in ESRD, combination pills cannot be used in ESRD (25).

Dosing of Hepatitis C Medications in Dialysis

For many years, interferon alfa was the only option available for treatment of HCV in dialysis patients. Due to significant adverse effects and relatively low sustained viral response (SVR) rate (~30%), it was not an appealing option for either physicians or patients. With the addition of low dose ribavirin, the SVR appears to approximate 60% (35), although concern for side effects, including severe anemia, persists. With the development of direct-acting antiviral agents (**Figure 1**), there is hope for improved efficacy; however, clinical data in dialysis patients are extremely limited. Dosing of approved agents is shown in **Table 2**.

Interferon alfa

The interferons bind to cells infected by HCV, activating expression of proteins that inhibit viral replication (36). Interferon alfa has been utilized to treat chronic hepatitis C since the late 1980s (37, 38). Pegylated interferon was approved by the FDA in 2001. Both pegylated interferon alfa-2a and 2b are eliminated by hepatic and renal routes (36). Clearance of

pegylated interferon alfa-2a is reduced by 25% to 45% in hemodialysis patients (39). Similarly, a study of pegylated interferon alfa-2b in subjects with varying degrees of renal impairment showed that clearance was reduced in proportion to kidney function (40); however, hemodialysis did not affect drug clearance. The recommended dosage of pegylated interferon alfa-2a in the dialysis population is 135 µg per week (39) (**Table 2**). For pegylated interferon alfa-2b, a 50% dose reduction is recommended in dialysis patients (36), although recent clinical trials of pegylated interferon and ribavirin in dialysis patients have used a dose of 1.0 µg per week (10).

Ribavirin

Ribavirin is a nucleoside analog that inhibits viral replication and protein synthesis (36). It may also have some immunomodulatory effects that augment the activity of interferon (41). Ribavirin has been used for decades to treat hepatitis C and other viral infections, but its use in individuals with chronic hepatitis C and significant renal impairment was just approved by the FDA in 2011 (42). Drug clearance occurs by both renal and hepatic routes (36). In moderate or severe renal dysfunction, ribavirin levels are significantly increased, necessitating dosage reduction. Significant amounts of drug are not removed with dialysis - a pharmacokinetic study in hemodialysis patients showed that only 2.4% of the drug was removed with a 4 hour dialysis session (43). The recommended dose in dialysis patients is 200 mg daily, although doses ranging from 86 mg to 260 mg daily have been used in pegylated interferon and ribavirin studies in this group of patients (35). In most clinical studies, ribavirin dosing has been decreased in response to worsening anemia (44, 45). As such, it appears that ribavirin can be used effectively and safely in dialysis patients with close monitoring of hemoglobin levels and appropriate adjustments of ribavirin and erythropoietin dosing (46).

Direct-acting antiviral agents

NS3/NS4 Protease Inhibitors—Boceprevir and telaprevir are first generation inhibitors of the NS3/NS4 protease that inhibit viral replication (8, 47). Both were approved by the FDA in May 2011 for the treatment of chronic HCV infection, genotype 1. Metabolism of boceprevir occurs by alpha-ketoreductases and CYP3A3 (48, 49). As shown in one study, renal elimination appears to be minimal, with < 10% of radiolabelled boceprevir recovered in the urine (50). No difference in boceprevir pharmacokinetics were observed between healthy subjects and hemodialysis patients after a single drug dose (50). In the same study, the amount of boceprevir removed with hemodialysis was small and not clinically significant (50). Thus, although the clinical experience with use of boceprevir in dialysis patients is extremely limited, no dosage adjustment appears necessary for ESRD. A clinical trial designed to assess the safety and efficacy of triple therapy with pegylated interferon, ribavirin and boceprevir in patients with chronic HCV infection (genotype 1) and ESRD on hemodialysis is currently underway (51).

Telaprevir appears to be primarily excreted in the feces (36). Available data suggest that impaired renal function does not significantly affect the pharmacokinetics of the drug (52-54). In a case series of French dialysis patients treated with standard doses of telaprevir, drug trough levels were similar to those observed in healthy volunteers (52). Another case

study showed that hemodialysis did not have a significant impact on the pharmacokinetics of telaprevir (54). The available data are not sufficient to recommend use of telaprevir in dialysis patients.

Simeprevir is a second generation NS3/4A protease inhibitor approved by the FDA in November 2013 for chronic hepatitis C genotype 1 (55). Elimination is primarily through biliary excretion into the feces (36). After a single dose of 200 mg of simeprevir was administered, less than 1% of the drug was excreted in the urine (56). As simeprevir is highly protein-bound, it is unlikely that significant amounts of drug will be removed by dialysis (56). Although it has not been studied in ESRD patients, no dosage adjustment is recommended for underlying kidney disease (36, 56).

A combination of a new NS3/4 protease inhibitor and an inhibitor of the non-structural protein 5A (NS5A) is currently being tested in patients with HCV and chronic kidney disease, including those on dialysis (57).

NS5B Polymerase Inhibitor—Sofosbuvir is a nucleotide analogue that inhibits the NS5B polymerase of the hepatitis C virus (58). In December 2013, sofosbuvir was approved by the FDA for treatment of chronic hepatitis C genotypes 1 through 4. Sofosbuvir is metabolized in the liver, but its main metabolite is excreted primarily in the urine (59, 60). A pharmacokinetic study showed that the metabolite significantly accumulates in severe renal impairment, although hemodialysis does remove a substantial amount of drug and its metabolite from plasma (61). Due to these factors, the safety of sofosbuvir in dialysis patients has yet to be established and a dosing recommendation cannot be made (8, 59). However, a phase 2b, open-label study of sofosbuvir and ribavirin in genotype 1 or 3 HCV-Infected patients with severe renal insufficiency and ESRD is currently recruiting patients (62).

Another trial is currently evaluating an interferon-free regimen consisting of ABT-450 (a protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), dasabuvir (a non-nucleoside polymerase inhibitor), with or without ribavirin in treatment-naïve adults with genotype 1 HCV who also have severe renal impairment or ESRD (RUBY-I) (63). Until the results of these ongoing trials are available, treatment options for HCV infection patients on dialysis will remain limited.

Considerations for the HIV-HCV co-infected individual

A number of interactions have been demonstrated between therapeutic agents used for those with HIV and HCV co-infection, making the therapeutic approach difficult and complex. Use of ribavirin in individuals taking didanosine is contraindicated due to potentially life-threatening mitochondrial toxicity (19). The combination of zidovudine and ribavirin is also not recommended due to increased risk of anemia (19).

Boceprevir, an inhibitor of CYP3A4 and OATP1B1 and 1B3 (36), is associated with reduced concentrations when administered with efavirenz (48, 64, 65). Thus, co-administration of these drug is not recommended (19). Drug interactions have also been observed between boceprevir and several HIV protease inhibitors, and this combination of

therapies is not recommended (19, 48). Significant drug interactions have not been observed with boceprevir co-administration with raltegravir, etravirine, maraviroc or dolutegravir (19, 66); however, raltegravir-based HIV regimens are currently recommended in individuals treated with boceprevir (48).

Telaprevir is both a substrate for and inhibitor of CYP3A4. Based on studies in HIV and HCV co-infected patients (67), telaprevir can be used in patients on atazanavir/ritonavir and efavirenz, although a higher dose of telaprevir is required in individuals taking efavirenz (19, 48). Use of telaprevir with darunavir, fosamprenavir, lopinavir, and rilpivirine is not recommended at this time (19, 48, 68). Combined use with etravirine and dolutegravir may be pursued cautiously (48).

Simeprevir is also an inhibitor of CYP3A4 (36). Drug levels decrease in individuals also taking efavirenz, and increase in individuals taking combined darunavir/ritonavir (48). A recent phase III clinical trial of simeprevir in HIV-HCV co-infected individuals excluded efavirenz and protease inhibitor regimens (69), and co-administration of simeprevir with any of the HIV protease inhibitors is not recommended (19). No significant interactions have yet been observed with the regimen of tenofovir, rilpivirine and raltegravir (48).

Conclusions

Safe and effective dosing of many HIV and HCV medications in the dialysis patient requires adjustments based on differences in their pharmacokinetics compared with those seen in individuals with normal kidney function. While the availability of direct antiviral agents for HCV has changed the standard of care for the general population, very limited data are available to guide treatment of HCV in dialysis patients. Moreover, drug interactions may make the treatment of the HIV-HCV co-infected dialysis patient challenging. Fortunately, many new agents are in development for treatment of these diseases, particularly for HCV (8, 58). Studies of these new drugs in ESRD patients on dialysis will be important to address the needs of this underserved population.

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Hepatitis C Genome

Structural genes					Non-structural genes					
C	E1	E2	p7	NS2	NS3	NS4A	NS4B	NS5A	NS5B	
					Mechanism	NS3/4A protease inhibition		Inhibition of NS5A/replication complex		NS5B polymerase inhibition
					Drugs	Telaprevir Boceprevir Simeprevir <i>Faldaprevir</i> <i>Asunaprevir</i> <i>ABT-450</i> <i>MK-5172</i>		<i>Daclatasvir</i> <i>Ledipasvir</i> <i>Ombitasvir</i>		Sofosbuvir <i>Dasabuvir</i> <i>BMS-791325</i>

Host Targets

Target	Cyclophilin A (host protein that interacts with NS5A)	MicroRNA-122 (host RNA involved in post-transcriptional gene regulation)
Mechanism	Cyclophilin A inhibition	miR-122 antagonism
Drugs	<i>Alisporivir</i> <i>SCY-635</i>	<i>Miravirsen</i>

Italics indicate drugs in development

Figure 1.

Targets of selected HCV therapies on the market and in development (8, 71-74)

Table 1

Recommended dosage of HIV treatments for end-stage renal disease (15, 19, 25, 70).

Drug	Class	Standard Dose	Dose in ESRD
Abacavir	NRTI	300 mg bid	300 mg bid
Didanosine	NRTI	60 kg: 200 mg bid EC 400 mg daily <60 kg: 125 mg bid EC 250 mg daily	60 kg: 100 mg daily EC 125 mg daily <60 kg: 75 mg daily EC - avoid use
Emtricitabine	NRTI	200 mg daily	200 mg every 96 hours *
Lamivudine	NRTI	150 mg bid or 300 mg daily	50 mg loading dose followed by 25 mg daily *
Stavudine	NRTI	60 kg: 40 mg bid <60 kg: 30 mg bid	60 kg: 20 mg daily * <60 kg: 15 mg daily *
Tenofovir	NRTI	300 mg daily	300 mg weekly *
Zalcitabine	NRTI	Not available in the United States	
Zidovudine	NRTI	300 mg bid or 200 mg tid	100 mg tid *
Delaviridine	NNRTI	400 mg tid	400 mg tid
Efavirenz	NNRTI	600 mg daily	600 mg daily
Etravirine	NNRTI	200 mg bid	200 mg bid
Nevirapine	NNRTI	200 mg daily for 2 weeks followed by 200 mg bid	200 mg daily for 2 weeks followed by 200 mg bid plus an additional 200 mg after hemodialysis
Rilpivirine	NNRTI	25 mg daily	25 mg daily
Atazanavir	PI	300 mg daily with ritonavir 100 mg daily	300 mg daily with ritonavir 100 mg daily (use only in treatment naive pts)
Darunavir	PI	800 mg daily or 600 mg bid	800 mg daily or 600 mg bid
Amprenavir	PI	Not available in the United States	
Fosamprenavir	PI	1400 mg bid	1400 mg bid
Indinavir	PI	800 mg tid	800 mg tid
Lopinavir/ritonavir	PI	400 mg/100 mg bid or 800 mg/200 mg daily	400 mg/100 mg bid, avoid once daily dosing
Nelfinavir	PI	750 mg tid or 1250 mg bid	750 mg tid or 1250 mg bid
Ritonavir	PI	100 mg to 400 mg per day to boost other PIs	100 mg to 400 mg per day
Saquinavir	PI	1000 mg bid (hard-gel) 1200 mg tid (soft-gel)	1000 mg bid (hard-gel) 1200 mg tid (soft-gel)
Tipranavir	PI	500 mg bid	500 mg bid
Dolutegravir	INSTI	50 mg daily or bid	50 mg daily or bid
Elvitegravir	INSTI	1 tab daily as Stribild	Contraindicated
Raltegravir	INSTI	400 mg bid	400 mg bid
Maraviroc	CCR5 antagonist	150 mg to 600 mg bid depending on concomitant medications	300 mg bid, use with CYP3A4 inducers/inhibitors not recommended
Enfuvirtide	Fusion inhibitor	90 mg bid	90 mg bid

bid = twice daily, tid = three times a day

* Dose after dialysis on dialysis days

Table 2

Recommended dosage for hepatitis C treatments for end-stage renal disease (36, 71).

Drug	Class	Standard Dose	Dose in ESRD
Peginterferon alfa 2a	Immunomodulator	180 µg weekly	135 µg weekly
Peginterferon alfa 2b	Immunomodulator	1.5 µg/kg weekly	0.75-1.0 µg/kg weekly *
Ribavirin	Nucleoside analog	400 mg or 600 mg twice daily	200 mg daily
Boceprevir	NS3/NS4 protease inhibitor	800 mg three times a day	800 mg three times a day
Telaprevir	NS3/NS4 protease inhibitor	1125 mg twice daily	1125 mg twice daily
Simeprevir	NS3/NS4 protease inhibitor	150 mg daily	150 mg daily
Sofosbuvir	NS5B polymerase inhibitor	400 mg daily	Use not recommended

* Not approved for use in combination with Rebetol in ESRD