Antiretroviral Dosing in Renal Impairment

Updated March 2016

Protease Inhibitors (PIs)

Antiretroviral	Usual adult dose	Considerations for renal impairment	Considerations for haemodialysis
Atazanavir Reyataz® hard capsules	300 mg once daily taken with ritonavir 100 mg once daily	No dosage adjustment is needed for atazanavir in renal impairment	Atazanavir use in haemodialysis patients is not recommended. Atazanavir pharmacokinetic parameters decreased by 30-50% in patients undergoing haemodialysis compared to patients with normal renal function.
Darunavir Prezista® tablets	*ART-naïve patients*: 800 mg with cobicistat 150 mg or ritonavir 100 mg, all once daily *ART-experienced patients (with no darunavir resistance, with plasma HIV-1 RNA <100,000 copies/ml and CD4 cell count ≥100)*: 800 mg with cobicistat 150 mg or ritonavir 100 mg, all once daily. *All other ART-experienced patients*: 600 mg + ritonavir 100 mg, both twice daily	No dose adjustment is required for darunavir/ritonavir in patients with renal impairment	As darunavir and ritonavir are highly bound to plasma proteins, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis. No special precautions or dose adjustments are required
Rezolsta® tablets: (darunavir/cobicistat 800/150 mg)		Cobicistat inhibits the tubular secretion of creatinine and may cause modest declines in creatinine clearance. Hence, the use of creatinine clearance as an estimate of renal elimination capacity may be misleading. Cobicistat as a pharmacokinetic enhancer of darunavir should, therefore, not be initiated in patients with CrCl <70 ml/min if any co-administered agent requires dose adjustment based on creatinine clearance: e.g. emtricitabine, lamivudine, tenofovir. Based on the very limited renal elimination of cobicistat and darunavir, no special precautions or dose adjustments of Rezolsta are required for patients with renal impairment.	Cobicistat has not been studied in patients receiving dialysis, and, therefore, no recommendation can be made for the use of darunavir/ cobicistat in these patients.
Fosamprenavir Telzir® film coated tablets	700 mg fosamprenavir twice daily with 100 mg ritonavir twice daily	No dose adjustment is considered necessary in patients with renal impairment	No specific recommendation
Indinavir Crixivan® hard capsules	800 mg every 8 hours or 400 mg with ritonavir 100 mg, both twice daily	Safety in patients with impaired renal function has not been studied; however, <20% of indinavir is excreted in the urine unchanged or as metabolites. Note: see product label for details on nephrolithiasis risk.	No specific recommendation
Lopinavir (with RTV) Kaletra® 200/50 mg film coated tablets	400/100 mg twice daily	Since the renal clearance of lopinavir and ritonavir is negligible, increased plasma concentrations are not expected in patients with renal impairment.	Because lopinavir and ritonavir are highly protein bound, it is unlikely that they will be significantly removed by haemodialysis or peritoneal dialysis.
Saquinavir Invirase® film coated tablets	1000 mg twice daily with ritonavir 100 mg twice daily	No dosage adjustment is necessary for patients with mild to moderate renal impairment. Caution should be exercised in patients with severe renal impairment	No specific recommendation
Tipranavir Aptivus® soft capsules	500 mg co-administered with 200 mg ritonavir twice daily	Tipranavir pharmacokinetics have not been studied in patients with renal impairment. Since the renal clearance of tipranavir is negligible, increased plasma concentrations are not expected in patients with renal impairment. No dosage adjustment is required.	No specific recommendation

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Antiretroviral Dosing in Renal Impairment

Updated March 2016

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Antiretroviral	Usual adult dose	Considerations for renal impairment	Considerations for haemodialysis
Efavirenz Sustiva®film coated tablets Generic tablets	600 mg once daily	The pharmacokinetics of efavirenz have not been studied in patients with renal insufficiency. <1% of a dose is excreted unchanged in the urine, so the impact of renal impairment on efavirenz elimination should be minimal. Close safety monitoring of patients with severe renal failure is recommended.	No specific recommendation
Etravirine Intelence® tablet)	200 mg twice daily	The pharmacokinetics of etravirine have not been studied in patients with renal insufficiency. <1.2% of the administered dose of etravirine is excreted in the urine. The impact of renal impairment on etravirine elimination is expected to be minimal. No dose adjustment is required in patients with renal impairment.	As etravirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis
Nevirapine Viramune® tablets Viramune® Prolonged Release Generic tablets	One 200 mg tablet daily for the first 14 days, followed by one 200mg tablet twice daily OR One 400 mg prolonged release tablet daily.	Renal impairment (mild, moderate and severe) resulted in no significant change in the pharmacokinetics of nevirapine. Patients with CrCl ≥20 ml/min do not require a dose adjustment	Patients with ESRD requiring dialysis exhibited a 43.5% reduction in nevirapine AUC over a one-week exposure period, and accumulation of nevirapine hydroxy-metabolites in plasma. For patients requiring dialysis an additional 200 mg dose of nevirapine following each dialysis treatment is recommended. For patients taking a prolonged release tablet, an extra 200 mg may be given as an immediate release preparation.
Rilpivirine Edurant® tablets	One 25 mg tablet once daily	No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease, rilpivirine should be used with caution. In patients with severe renal impairment or end-stage renal disease, the combination of rilpivirine with a strong CYP3A inhibitor (e.g. ritonavir-boosted HIV protease inhibitor) should only be used if the benefit outweighs the risk. Treatment with rilpivirine may result in an early small increase of mean serum creatinine levels which is not considered clinically relevant	As rilpivirine is highly bound to plasma proteins, it is unlikely that it will be significantly removed by haemodialysis or peritoneal dialysis

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Antiretroviral Dosing in Renal Impairment

Updated March 2016

Nucleoside/tide Reverse Transcriptase Inhibitors (1/2)

<table>
<tr><th>Antiretroviral</th><th>Usual adult dose</th><th>Considerations for renal impairment</th><th>Considerations for haemodialysis</th></tr>
<tr><td>Abacavir
Ziagen®
film coated tablets</td><td>300 mg twice daily
OR
600 mg once daily</td><td>No dosage adjustment of abacavir is necessary in patients with renal dysfunction. Abacavir is not recommended for patients with end-stage renal disease.</td><td>No specific recommendations</td></tr>
<tr><td>Didanosine
Videx® EC capsules
Videx® chewable tablets</td><td>≥60kg: 400 mg once daily
OR 200 mg twice daily

<60kg: 250 mg once daily
OR 125 mg twice daily</td><td>Patients with a creatinine clearance <60 ml/min may be at greater risk of didanosine toxicity due to decreased drug clearance. A dose reduction is recommended for these patients.
<table>
<tr><th rowspan="2">Creatinine Clearance (ml/min)</th><th colspan="2">Total Daily Dose</th></tr>
<tr><th>≥60 kg</th><th><60kg</th></tr>
<tr><td>at least 60</td><td>400 mg</td><td>250 mg</td></tr>
<tr><td>30 – 59</td><td>200 mg</td><td>150 mg*</td></tr>
<tr><td>10 – 29</td><td>150 mg*</td><td>100 mg*</td></tr>
<tr><td>less than 10</td><td>100 mg*</td><td>75 mg*</td></tr>
</table>
*Once daily regimens only</td><td>The half-life of didanosine after oral administration increased from 1.4 hours in subjects with normal renal function to 4.1 hours in subjects with severe renal impairment requiring dialysis. After an oral dose, didanosine was not detectable in peritoneal dialysis fluid; recovery in haemodialysate ranged from 0.6% to 7.4% of the dose over a 3-4 hour dialysis period. The dose should be taken after dialysis, however it is not necessary to take a supplemental dose following haemodialysis.</td></tr>
<tr><td>Emtricitabine
Emtriva® hard capsules
Emtriva® oral solution</td><td>200 mg once daily</td><td>Emtricitabine is eliminated by renal excretion and exposure was significantly increased in patients with renal insufficiency. Dose OR dose interval adjustment is required in all patients with creatinine clearance <50 ml/min. Clinical response to treatment & renal function should be closely monitored.
<table>
<tr><th></th><th colspan="4">Creatinine Clearance (ml/min)</th></tr>
<tr><th></th><th>≥50</th><th>30-49</th><th>15-29</th><th><15 (intermittent haemodialysis)</th></tr>
<tr><td>Dose interval for 200 mg hard capsules</td><td>200 mg every 24 h</td><td>200 mg every 48 h</td><td>200 mg every 72 h</td><td>200 mg every 96 h</td></tr>
<tr><td>Dose of 10 mg/ml oral solution</td><td>240 mg (24 ml) every 24 h</td><td>120 mg (12 ml) every 24 h</td><td>80 mg (8 ml) every 24 h</td><td>60 mg (6 ml) every 24 h</td></tr>
</table></td><td>Dosing for intermittent dialysis assumes a 3h haemodialysis session three times weekly; at least 12h after administration of the last dose of emtricitabine. In patients with ESRD on haemodialysis, ~30% of the emtricitabine dose was recovered in dialysate over a 3h dialysis period, started within 1.5 hours of emtricitabine dosing (blood flow rate of 400 ml/min and dialysate flow rate of ~600ml/min). Patients managed with other forms of dialysis such as ambulatory peritoneal dialysis have not been studied and dose recommendations cannot be made.</td></tr>
<tr><td>Lamivudine
Epivir®
film coated tablets</td><td>300 mg once daily
OR
150 mg twice daily</td><td>Lamivudine concentrations are increased in patients with moderate-severe renal impairment due to decreased clearance.
<table>
<tr><th>Creatinine clearance (ml/min)</th><th>First dose</th><th>Maintenance dose</th></tr>
<tr><td>≥50</td><td>300 mg or 150 mg</td><td>300 mg once daily or 150 mg twice daily</td></tr>
<tr><td>30-<50</td><td>150 mg</td><td>150 mg once daily</td></tr>
<tr><td>15 to <30</td><td>150 mg</td><td>100 mg once daily*</td></tr>
<tr><td>5 to <15</td><td>150 mg</td><td>50 mg once daily*</td></tr>
<tr><td><5</td><td>50 mg*</td><td>25 mg once daily*</td></tr>
</table>
* Use oral solution for doses <150 mg</td><td>No specific recommendation</td></tr>
</table>

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Antiretroviral Dosing in Renal Impairment

Updated March 2016

Nucleoside/tide Reverse Transcriptase Inhibitors (2/2)

<table>
<tr><th>Antiretroviral</th><th>Usual adult dose</th><th>Considerations for renal impairment</th><th>Considerations for haemodialysis</th></tr>
<tr><td>Stavudine
Zerit® hard capsules</td><td>≥60kg: 40 mg twice daily
<60kg: 30 mg twice daily</td><td>The clearance of stavudine decreases as creatinine clearance decreases; therefore, it is recommended that the dosage of stavudine be adjusted in patients with reduced renal function.
<table>
<tr><th>Creatinine Clearance (ml/min)</th><th colspan="2">Stavudine Dose</th></tr>
<tr><td></td><td><60 kg</td><td>≥60 kg</td></tr>
<tr><td>26-50</td><td>15 mg twice daily</td><td>20 mg twice daily</td></tr>
<tr><td>≤25</td><td>15 mg every 24 h</td><td>20 mg every 24 h</td></tr>
</table></td><td>Patients on haemodialysis should take stavudine after the completion of haemodialysis, and at the same time on non-dialysis days</td></tr>
<tr><td>Tenofovir
Viread®
film coated tablets</td><td>245 mg once daily</td><td>In patients with renal impairment tenofovir should only be used if the potential benefits of treatment outweigh potential risks.
Mild renal impairment (CrCl 50-80 ml/min): Limited data from clinical studies support once daily dosing of 245 mg tenofovir.
Moderate renal impairment (CrCl 30-49 ml/min): 132mg (4 scoops) tenofovir 33mg/g granules once daily OR one 245mg tablet every 48 hours can be used.
Severe renal impairment (CrCl <30 ml/min):
CrCl 20-29 ml/min: 65 mg (2 scoops) tenofovir 33mg/g granules once daily.
CrCl 10-19 ml/min: 33 mg (1 scoop) tenofovir 33 mg/g granules once daily OR one 245mg tablet every 72-96 h (dosing twice a week).
Clinical response and renal function should be closely monitored.
Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of tenofovir in clinical practice. Monitoring of renal function is recommended.
No dosing recommendations can be given for non-haemodialysis patients with CrCl <10 ml/min.</td><td>16.5 mg (0.5 scoop) tenofovir 33 mg/g granules given following completion of each 4-hour haemodialysis session OR one 245 mg tenofovir tablet taken every 7 days following completion of a haemodialysis session; assuming three haemodialysis sessions per week, each of approximately 4 hours duration or after 12 hours cumulative haemodialysis.
No dosing recommendations can be given for non-haemodialysis patients with CrCl <10 ml/min.</td></tr>
<tr><td>Zidovudine
Retrovir® capsules
Generic capsules</td><td>250 mg or 300 mg twice daily</td><td>In patients with severe renal impairment, apparent zidovudine clearance after oral administration was ~50% of that reported with normal renal function.
For patients with severe renal impairment (CrCl <10 ml/min), the recommended dose is 100 mg every 6-8 h (300-400 mg daily).
Haematological parameters and clinical response may influence the need for subsequent dosage adjustment</td><td>Haemodialysis and peritoneal dialysis have no significant effect on zidovudine elimination whereas elimination of the inactive glucuronide metabolite is increased.
For patients with end-stage renal disease maintained on haemodialysis or peritoneal dialysis, the recommended dose is 100 mg every 6-8 h (300-400 mg daily).</td></tr>
</table>

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Antiretroviral Dosing in Renal Impairment

Entry/Integrase Inhibitors

Antiretroviral	Usual adult dose	Considerations for renal impairment	Considerations for haemodialysis
Dolutegravir Tivicay® film coated tablets	*Patients with HIV-1 without documented or suspected resistance:* 50 mg once daily (twice daily when taken with e.g. efavirenz, nevirapine). *Patients with HIV-1 with resistance to the integrase class (documented or suspected)*: 50 mg twice daily.	No dosage adjustment is required in patients with mild, moderate or severe (CrCl <30 ml/min, not on dialysis) renal impairment. Exposure to dolutegravir was decreased by ~40% in subjects with severe renal impairment. The mechanism is unknown.	No data are available in subjects receiving dialysis although differences in pharmacokinetics are not expected in this population
Elvitegravir Vitekta® film coated tablets	85 mg once daily with ATV/r or LPV/r *OR* 150 mg once daily with DRV/r or FPV/r)	No dose adjustment is required for patients with renal impairment. No clinically relevant differences in elvitegravir pharmacokinetics were observed between subjects with severe renal impairment and healthy subjects.	No specific recommendation
Maraviroc Celsentri® film coated tablet	150 mg, 300 mg or 600 mg twice daily, depending on interactions with co-administered antiretroviral therapy and other medicinal products	Exposures in subjects with severe renal impairment and ESRD were within the range observed in single maraviroc 300mg dose studies with normal renal function. No dose adjustment is necessary in patients with renal impairment receiving maraviroc **WITHOUT** a potent CYP3A4 inhibitor. In patients with CrCl <80 mL/min, who are also receiving potent CYP3A4 inhibitors, the dose interval of maraviroc should be adjusted to 150 mg **ONCE** daily. An increased risk of postural hypotension may occur in patients with severe renal insufficiency who are treated with potent CYP3A inhibitors and maraviroc. Maraviroc should be used with caution in patients with severe renal impairment (CrCl <30 mL/min) who are receiving potent CYP3A4 inhibitors.	Dialysis had a minimal effect on exposure in subjects with ESRD
Raltegravir Isentress® film coated tablets	400 mg twice daily	No dosage adjustment is required for patients with renal impairment. Renal clearance of unchanged medicinal product is a minor pathway of elimination. In adults, there were no clinically important pharmacokinetic differences between patients with severe renal insufficiency and healthy subjects	Because the extent to which raltegravir may be dialysable is unknown, dosing before a dialysis session should be avoided.

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Antiretroviral Dosing in Renal Impairment

Updated March 2016

Fixed Dose Combinations *(Caution required as individual drugs in a FDC may require dose modification)*

Antiretroviral	Usual adult dose	Considerations for renal impairment	Considerations for haemodialysis
Atripla® TDF-FTC-EFV	One tablet daily	Atripla is not recommended for patients with moderate or severe renal impairment (CrCl <50 ml/min). Patients with moderate or severe renal impairment require dose interval adjustment of emtricitabine and tenofovir disoproxil fumarate that cannot be achieved with the combination tablet. As Atripla may cause renal damage, monitoring of renal function is recommended.	No specific recommendation
Combivir® 3TC-ZDV	One tablet twice daily	Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. Therefore as dosage adjustment of these may be necessary it is recommended that separate preparations of lamivudine and zidovudine be administered to patients with reduced renal function (CrCl ≤50 ml/min).	No specific recommendation
Eviplera® TDF-FTC-RPV	One tablet daily	Treatment with Eviplera resulted in an early small increase of serum creatinine levels which is not considered clinically relevant. Limited data from clinical studies support use of Eviplera in patients with mild renal impairment (CrCl 50-80 mL/min). Long-term safety data for emtricitabine and tenofovir have not been evaluated in patients with mild renal impairment: Eviplera should only be used if potential benefits of treatment outweigh risks. Eviplera is not recommended for patients with moderate or severe renal impairment (CrCl <50 ml/min). Such patients require a dose interval adjustment of emtricitabine and tenofovir that cannot be achieved with the combination tablet.	No specific recommendation
Genvoya® TAF-FTC-EVG-COBI	One tablet daily	No dose adjustment of Genvoya is required in adults or adolescents (≥12 years and ≥35 kg) with CrCl ≥30 ml/min. Genvoya should not be initiated in patients with CrCl <30 ml/min as there are insufficient data available regarding the use of Genvoya in this population. Genvoya should be discontinued in patients with CrCl that declines below 30 ml/min during treatment	No specific recommendation
Kivexa® ABC-3TC	One tablet daily	Kivexa is not recommended for use in patients with a creatinine clearance <50 ml/min as necessary dose adjustment cannot be made	No specific recommendation
Stribild® TDF-FTC-EVG-COBI	One tablet daily	Stribild should not be initiated in patients with CrCl <70 ml/min. Stribild should be discontinued if CrCl declines <50 ml/min during treatment with Stribild as dose interval adjustment is required for emtricitabine and tenofovir and this cannot be achieved with the fixed-dose combination tablet. CrCl, serum phosphate, urine glucose and urine protein should be monitored every four weeks during the first year and then every three months during Stribild therapy. In patients at risk for renal impairment a more frequent monitoring of renal function is required.	No specific recommendation
Triumeq® ABC-3TC-DTG	One tablet daily	Triumeq is not recommended for patients with a creatinine clearance <50 ml/min.	No specific recommendation
Trizivir® ABC-3TC-ZDV	One tablet twice daily	Lamivudine and zidovudine concentrations are increased in patients with renal impairment due to decreased clearance. As dose adjustments may be necessary, it is recommended that separate preparations of abacavir, lamivudine and zidovudine be administered to patients with reduced renal function (CrCl ≤50 ml/min). Trizivir should not be administered to patients with end-stage renal disease	No specific recommendation
Truvada® TDF-FTC	One tablet daily	Emtricitabine and tenofovir exposure increases in patients with renal dysfunction. There are limited data on the safety and efficacy of Truvada in patients with moderate and severe renal impairment (CrCl <50 ml/min) and long-term safety data has not been evaluated for mild renal impairment (CrCl 50-80 ml/min). In patients with renal impairment, Truvada should only be used if the potential benefits of treatment outweigh the risks. Patients with renal impairment require close monitoring of renal function. Dose interval adjustments are recommended for patients with CrCl 30-49 ml/min, which require separate preparations.	No specific recommendations

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