Dosing of *Triumeq* in Patients with Renal Impairment

Summary

- *Triumeq* (abacavir/dolutegravir/lamivudine [ABC/DTG/3TC]) is not recommended for patients with impaired renal function (creatinine clearance < 30 mL/min) because ABC/DTG/3TC is a fixed-dose combination and the dosage of the individual components cannot be adjusted.[1]
- If a dose reduction of lamivudine (3TC), a component of ABC/DTG/3TC, is required for patients with creatinine clearance < 30 mL/min, then the individual components (ABC/DTG/3TC) should be used.
- Several pharmacokinetic (PK) studies have evaluated the effect of various degrees of renal impairment on the PK of 3TC.[2-8] Study results conclude that decreasing renal function is associated with reduced 3TC clearance; therefore, dosage adjustment is required in patients with impaired renal function.
- Important safety information and boxed warning(s) can be found in the Prescribing Information link and can also be accessed at Our HIV Medicines.

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ABC/DTG/3TC LABEL RECOMMENDATIONS

ABC/DTG/3TC is not recommended for patients with impaired renal function (creatinine clearance < 30 mL/min) because ABC/DTG/3TC is a fixed-dose combination and the dosage of the individual components cannot be adjusted.[1] If a dose reduction of 3TC, a component of ABC/DTG/3TC, is required for patients with creatinine clearance < 30 mL/min, then the individual components (ABC, DTG, and 3TC) should be used.

COMPONENTS OF ABC/DTG/3TC

Abacavir

No dosage adjustment of abacavir is necessary in patients with renal dysfunction.[9] ABC is predominantly metabolized by the liver, with subsequent excretion of metabolites primarily in the urine. Approximately 2% of the administered dose of abacavir is excreted unchanged in the urine.

PK Profile of ABC in Renal Impairment

A PK study was conducted in five HIV-1 infected adults with varying degrees of renal insufficiency (creatinine clearance 60, 40, 25, 20 mL/min and one patient on hemodialysis).[10] All patients had previously been treated with combination antiretroviral therapy, including ABC (300 mg or 600 mg) for at least two months. Plasma concentrations were determined post-dose, after an overnight fast. The PK properties of ABC, including AUC, Cmax, Tmax, and half-life, were similar to those in patients with normal renal function. Approximately 24% of the dose was removed by a four-hour hemodialysis session.

Dolutegravir

DTG plasma concentrations were decreased in patients with severe renal impairment compared with those in matched healthy controls.[11] The table below summarizes the recommendations for use of DTG in patients with renal impairment.

Table 1. Recommendations for the Use of DTG in Renal Impairment[11]

Treatment-naive patients **Treatment-experienced, INSTI-naïve patients**	No dosage adjustment for mild/moderate/severe renal impairment
INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance)	No dosage adjustment for mild/moderate renal impairment
	In severe renal impairment, caution is warranted, as the decrease in DTG concentrations may result in loss of therapeutic effect and development of resistance to DTG or other coadministered antiretroviral agents. Please refer to the DTG local label for further information.

Severe renal impairment = CrCl < 30 mL/min

Use of DTG in Patients Receiving Hemodialysis

A single-center, single-arm, open-label study was conducted in five anuric HIV-infected patients (four men, one woman) with end stage renal disease undergoing hemodialysis to determine the effect of hemodialysis on DTG concentrations.[12] DTG 50 mg once daily was administered in the morning for five days, separated from any other drugs that could potentially alter DTG absorption. On day five, DTG concentrations were determined in blood samples at the beginning and end of a dialysis session, and one hour following initiation of dialysis from blood samples that entered into and exited from the dialyzer, as well as the dialysate. Due to the high protein binding profile of DTG, post-dialyzer concentrations (C_{out}) were corrected for hemoconcentration by a factor (F) based on total protein (TP) concentration pre- and post-dialyzer: $F = TP_{in}/TP_{out}$.

Three patients used conventional hemodialysis and two patients underwent online hemodiafiltration (OL-HDF). The duration of each hemodialysis session was approximately four hours, with a constant blood flow of 300 ml/min (conventional) or 400 ml/min (OL-HDF). All patients had a constant dialysate flow of 500 ml/min.

Study results showed that the median (range) hemodialysis extraction ratio was 7% (1–25) with negligible DTG concentrations in the dialysate. Additionally, at the end of the dialysis session, DTG concentrations in the plasma remained at 34 times above the protein-binding-adjusted 90% inhibitory concentration against different strains of HIV (IC90, 0.064 mg/L).

Lamivudine

3TC is predominantly eliminated unchanged in the urine.[13] The table below summarizes the recommendations for use of 3TC in patients with renal impairment.

Table 2. 3TC: Dosage Adjustments in Patients with Renal Impairment (Adults and Adolescents Weighing at least 30 kg)[13]

CrCl (mL/min)	Recommended Dose of 3TC
≥ 50	150 mg twice daily or 300 mg once daily
30–49	150 mg once daily
15–29	150 mg first dose, then 100 mg once daily
5–14	150 mg first dose, then 50 mg once daily
< 5	50 mg first dose, then 25 mg once daily

PK Profile of 3TC in Renal Impairment

Heald et al.[2]

PK parameters of 3TC were evaluated after a single, 300–mg dose of 3TC in patients with varying degrees of renal function (normal, moderate, and severe renal impairment).[2] As renal function decreased, the AUC (moderate/normal P < 0.0001; severe/normal P < 0.0001), Cmax (moderate/normal P = 0.014; severe/normal P < 0.0001), and half-life (moderate/normal P = 0.27; severe/normal P = 0.0026) were observed to increase, and Tmax did not significantly change.

Table 3. Heald et al. PK Findings of 3TC in Renal Impairment[a][2]

	CrCl: ≥ 60 ml/min (N = 6)	CrCl: 10 to 40 ml/min (N = 4)	CrCl: < 10 ml/min (N = 6)[b]
Cmax (mcg/mL)	2.5	3.5	5.7
Tmax (hr)	~1	~1	~2
AUC (mcg-h/mL)	10.9	45.7	146.5
t 1/2 (hr)	11.5	14.1	20.7

[a] All values reported are geometric mean, except for Tmax. [b] Three of the six received hemodialysis and the other three received peritoneal dialysis

Johnson et al.[3]

The PK of a single dose of 3TC administered to HIV negative patients with varying degrees of renal function was studied. The 29 patients were categorized into groups based of creatinine clearance (CrCl). Nine patients who had a CrCl of 82-117 ml/min received a 300-mg oral dose of 3TC, eight patients with a CrCl of 25-49 ml/min received a 300-mg oral dose of 3TC, and six patients with a CrCl of 13-19 ml/min received a 100-mg oral dose of 3TC. Decreasing renal function was associated with reduced 3TC clearance in a linear relationship.

Six additional patients who underwent hemodialysis received a 100-mg oral dose of 3TC approximately 2 hours prior to a 4-hour hemodialysis session and another 100-mg dose of 3TC 1 to 2 days after hemodialysis. Multiple blood samples were collected up to 48 hours post-dose. The AUC of 3TC was reduced by a mean of 24% after 4 hours of hemodialysis.

Bohjanen et al.[4]

This was as an open-label, single center study where all study participants had received 3TC for at least three months prior to enrollment into the study with varying 3TC dosing regimens. The PK of 3TC were studied in nine HIV-infected patients who were undergoing hemodialysis (with GFS-20 dialysis membranes) and had been receiving 150 mg of 3TC once daily for at least 2 weeks. Steady-state serum concentrations were measured over a 24-hour period on 2 consecutive days. Hemodialysis was performed on the first day approximately 20 hours after the first dose of 3TC, and the second dose of 3TC was given following hemodialysis. Approximately 28 mg of 3TC was removed by hemodialysis, however Cmax and

AUC were not significantly different after hemodialysis (3.24 mcg/mL and 46.5 mcg·h/mL, respectively) compared with before hemodialysis (3.77 mcg/mL and 49.8 mcg·h/mL, respectively). The mean serum concentrations of 3TC immediately increased after hemodialysis, prior to the administration of the second dose of 3TC.

Two additional patients were analyzed who underwent chronic ambulatory peritoneal dialysis (CAPD). Approximately 24mg of 3TC was removed by CAPD, however Cmax and AUC were not significantly different after CAPD compared with before CAPD. The mean serum concentrations of 3TC immediately increased after CAPD, prior to the administration of the second dose of 3TC.

Asari et al.[5]

The removal of 3TC by peritoneal dialysis was evaluated in 12 HIV-negative patients with severe renal dysfunction. Six patients undergoing automated peritoneal dialysis and six patients undergoing CAPD received 3TC 10 mg once daily for 8 days. Clearance of 3TC by peritoneal dialysis was approximately 1/15 to 1/30 of plasma clearance, which suggested that peritoneal dialysis did not significantly contribute to the overall clearance of 3TC.

Bouazza et al.[6]

A population PK analysis was performed in 244 HIV-positive patients (344 plasma concentrations) to estimate 3TC PK in patients with varying degrees of renal impairment. Serum creatinine clearance values for these patients were as follows: 177 had normal renal function (CrCl > 90 mL/min), 50 patients had mild renal impairment (CrCl = 60–90 mL/min), 20 patients had moderate renal impairment (CrCl = 30–60 mL/min), and 5 patients had severe renal impairment (CrCl < 30 mL/min). A two-compartment model adequately described the data. Results were as follows: apparent clearance (Cl/F) = 29.7 L/hr (32%), central (Vc/F) volume of distribution = 68.2 L, peripheral volumes of distribution (Vp/F) = 114 L, intercompartmental clearance (Q/F) = 10.1 L/hr (85%), and absorption rate constant, Ka (h-1) = 1. Clearance of 3TC corresponded to renal function.

Fischetti et al.[7]

A cross-sectional, single-center study was performed in HIV-1-infected adults (≥ 18 years) who were receiving 3TC as part of their ART for at least three months. The 34 patients were categorized into groups based of creatinine clearance (CrCl) and dosed based of institution guidelines. Five patients who had a CrCl > 50 ml/min received a 300-mg oral dose of 3TC, sixteen patients with a CrCl of 30-49 ml/min received a 300-mg oral dose of 3TC, three patients with a CrCl of 15-29 ml/min received a 150-mg oral dose of 3TC, ten patients who had a CrCl of < 15 ml/min or hemodialysis received 100 or 150 mg oral dose of 3TC. Serum concentrations were drawn, then patients were instructed to take 3TC and a second serum concentration was drawn (0.5-1.5 hrs post dose). The observed Cmax levels were comparable among CrCl cohorts, adjusting for the dose given. No adverse events were reported.

Izzedine et al.[8]

A single case report described the use of 3TC 150 mg every 12 hours for six months in an HIV-infected patient with ESRD on hemodialysis. The use of the normal dose of lamivudine resulted in concentrations much higher than those reported in patients with no renal impairment. No adverse events were reported.

REAL WORLD EVIDENCE OF ABC/DTG/3TC USE IN RENAL DYSFUNCTION

Please see following publication: [14]

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Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

REFERENCES

1. ViiV Healthcare. Global Data Sheet for abacavir/dolutegravir/lamivudine, Version 0019, August 17, 2023.
2. Heald AE, Hsyu PH, Yuen GJ, Robinson P, Mydlow P, Bartlett JA. Pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with renal dysfunction. *Antimicrob Agents Chemother.* 1996;40(6):1514-1519
3. Johnson MA, Verpooten GA, Daniel MJ, et al. Single dose pharmacokinetics of lamivudine in subjects with impaired renal function and the effect of haemodialysis. *British Journal of Clinical Pharmacology.* 1998;46(1):21-27. doi:http://dx.doi.org/10.1046/j.1365-2125.1998.00044.x.
4. Bohjanen PR, Johnson MD, Szczech LA, et al. Steady-state pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with end-stage renal disease receiving chronic dialysis. *Antimicrobial Agents and Chemotherapy.* 2002;46(8):2387-2392. doi:http://dx.doi.org/10.1128/AAC.46.8.2387-2392.2002.
5. Asari A, Iles-Smith H, Chen YC, et al. Pharmacokinetics of lamivudine in subjects receiving peritoneal dialysis in end-stage renal failure. *British Journal of Clinical Pharmacology.* 2007;64(6):738-744. doi:http://dx.doi.org/10.1111/j.1365-2125.2007.02963.x.
6. Bouazza N, Treluyer JM, Ghosn J, et al. Evaluation of effect of impaired renal function on lamivudine pharmacokinetics. *Br J Clin Pharmacol.* 2014;78(4):847-854. doi:http://dx.doi.org/10.1111/bcp.12407.
7. Fischetti B, Shah K, Taft DR, Berkowitz L, Bakshi A, Cha A. Real-World Experience With Higher-Than-Recommended Doses of Lamivudine in Patients With Varying Degrees of Renal Impairment. *Open Forum Infectious Diseases.* 2018;5(10):ofy225-ofy225. doi:http://dx.doi.org/10.1093/ofid/ofy225.
8. Izzedine H, Launay-Vacher V, Deray G. Dosage of Lamivudine in a Haemodialysis Patient. *Nephron.* 2000;86(4):553-553. doi:http://dx.doi.org/10.1159/000045870.
9. ViiV Healthcare, Global Data Sheet for abacavir, Version 33, June 20, 2022.
10. Izzedine H, Launay-Vacher V, Aymard G, Legrand M, Deray G. Pharmacokinetics of abacavir in HIV-1-infected patients with impaired renal function. *Nephron.* 2001;89(1):62-67. doi:http://dx.doi.org/10.1159/000046045.
11. ViiV Healthcare. Global Data Sheet for dolutegravir, Version 0015, October 12, 2018.
12. Moltó J, Graterol F, Miranda C, et al. Removal of dolutegravir by hemodialysis in HIV-Infected patients with end-stage renal disease. *Antimicrobial Agents and Chemotherapy.* 2016;60(4):2564-2566. doi:http://dx.doi.org/10.1128/AAC.03131-15.
13. ViiV Healthcare. Global Data Sheet for lamivudine, Version 0024, May 14, 2018.
14. Michienzi SM, Schriever CA, Badowski ME. Abacavir/lamivudine/dolutegravir single tablet regimen in patients with human immunodeficiency virus and end-stage renal disease on hemodialysis. *International journal of STD & AIDS.* 2019;30(2):181-187. doi:http://dx.doi.org/10.1177/0956462418800865.