

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, Vol. 30(2) 181–187

© The Author(s) 2018

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0956462418800865

journals.sagepub.com/home/std



Sarah M Michienzi¹ , Christopher A Schriever² and
Melissa E Badowski¹

Abstract

No single-tablet antiretroviral (ARV) regimens (STRs) are approved for patients with human immunodeficiency virus (HIV) and end-stage renal disease (ESRD) on hemodialysis (HD). Based on known pharmacokinetic (PK) properties, abacavir (ABC)/lamivudine (3TC)/dolutegravir (DTG) STR may represent a promising option. This case series presents the safety and efficacy of ABC/3TC/DTG STR in patients with HIV and ESRD on HD. Patients were included if they were HIV-positive, maintained on intermittent HD for ESRD, switched to an ARV regimen containing ABC/3TC/DTG, and had at least one set of virologic data before and after the switch. Average age (\pm standard deviation) was 59 (\pm 8) years. The majority of patients were cis-gender male and non-Hispanic Black. Only one demonstrated clinically significant resistance at baseline. All were on multiple-tablet regimens prior to the switch. Five patients (83%) achieved undetectable HIV-RNA after the switch while only four patients (46%) were undetectable immediately prior. No decline in immune function was noted. ABC/3TC/DTG STR was well tolerated. Only one patient self-reported an adverse event (nausea), which resolved without drug discontinuation. Based on these data, it appears that ABC/3TC/DTG may be a safe and effective ARV-STR option for patients with HIV and ESRD on HD. A larger trial including a PK analysis is needed to confirm these findings.

Keywords

Combination antiretroviral therapy, antiretroviral therapy, treatment, human immunodeficiency virus, acquired immunodeficiency syndrome

Date received: 5 May 2018; accepted: 20 August 2018

Introduction

Currently, there are several single-tablet antiretroviral (ARV) regimens (STRs) approved by the Food and Drug Administration for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. However, none are currently approved for use in patients with HIV and end-stage renal disease (ESRD) on hemodialysis (HD).¹

At this time, abacavir/lamivudine/dolutegravir (ABC/3TC/DTG) STR is not recommended in patients with a creatinine clearance (CrCl) less than 50 mL/min due to the need for dose adjustment of the lamivudine (3TC) component in renal impairment.¹ However, in practice, many clinicians take advantage of 3TC's

wide therapeutic index, as well as its favorable side effect profile and prescribe higher than recommended doses (up to the standard daily dose of 300 mg) in

¹Department of Pharmacy Practice, Section of Infectious Diseases Pharmacotherapy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

²Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Rockford, IL, USA

Corresponding author:

Sarah M Michienzi, Department of Pharmacy Practice, Section of Infectious Diseases Pharmacotherapy, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood St., Room 164 (MC 886), Chicago, IL 60612, USA.

Email: msarah@uic.edu

patients with renal impairment.²⁻⁵ This allows for decreased pill burden and, consequently, regimen simplification. Clinicians may have embraced this practice in the hope of avoiding the use of 3TC oral solution, typically required to achieve the recommended dose adjustment for HD. Therefore, the use of standard dose 3TC in HD is of particular interest given the availability of 3TC in an STR along with ABC and DTG, both not requiring renal dose adjustment.

In patients with normal renal function, the majority of 3TC (~70% in 24 h) is excreted unchanged via the urine.^{6,7} Because of this, renal function significantly affects the pharmacokinetics (PK) of 3TC demonstrating increases in area under the curve (AUC), half-life ($t_{1/2}$), and peak serum concentration (C_{max}) in patients with impaired vs. normal renal function.^{3,4,6} The linear relationship between clearance and renal function observed in initial PK studies^{4,6} led to current dosing recommendations for patients with impaired renal function,⁶ referenced in the package insert, along with the United States Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (US DHHS Guidelines).^{1,2} These recommendations were later confirmed by a PK modeling study.⁸

3TC is removed by a three and a half to four hour HD session with a mean clearance ranging from 106 mL/min (92–121 mL/min)⁴ to 138 mL/min (61–191 mL/min)³ as reported in the literature. However, due to the large volume of distribution and rapid redistribution of 3TC occurring after HD, a standard HD session does not clinically impact 3TC exposure.^{3,4} Therefore, further dose reductions of 3TC for HD are not recommended.⁴ For example, a dose of 25 mg daily for patients receiving HD provided similar levels to 150 mg twice daily in patients with normal renal function.³

Unlike 3TC, abacavir (ABC) is hepatically metabolized primarily via alcohol dehydrogenase and glucuronyl transferase into glucuronide and carboxylate metabolites.⁹ These metabolites are primarily excreted inactive in the urine and have little to no antiviral activity or associated toxicities.^{10,11} Less than 2% of ABC is excreted unchanged in the urine.^{9,12} Although the majority of ABC's PK data comes from preclinical trials, including studies in patients with normal renal function, there is little reason to believe alterations in renal function would adversely affect the PK.¹¹ Two small studies in patients with impaired renal function support these initial ABC PK findings. Both studies confirmed no alterations in absorption, elimination, or distribution occurred in patients with impaired vs. intact renal function.^{10,11} Therefore, no adjustment of ABC dose is recommended for patients with renal impairment, including those on HD.¹ Of note, a dose reduction is recommended for mild hepatic impairment

and it is contraindicated in moderate to severe hepatic impairment, as well as those who are HLA-B*5701 positive.^{1,13}

Metabolism of dolutegravir (DTG) occurs in the liver via glucuronidation by UGT1A1 and to a lesser extent by CYP3A4. The primary metabolite, DTG-glucuronide, is inactive and excreted along with other minor metabolites via the urine. Renal elimination accounts for ~30% of a DTG dose, with <1% as unchanged drug. In contrast, fecal elimination accounts for ~65% of a dose, with ~53% as unchanged drug.¹⁴ Impaired renal function is associated with reductions in both C_{max} and AUC compared to normal renal function, which may be attributed to alterations in absorption; however, these changes are considered clinically insignificant. DTG is minimally removed by HD as evidenced by a low HD extraction ratio (median ER = 7% in one study¹⁵ and ER = 0.0006 in one case report¹⁶), minimally to undetectable DTG concentrations in dialysate fluid, and plasma concentrations remaining above the protein-binding-adjusted inhibitory concentration.^{15,16} No adjustment of DTG is recommended for patients with renal impairment, including those on HD.¹ DTG has been associated with mild increases in serum creatinine due to inhibition of tubular secretion of creatinine. However, this increase is benign and does not affect glomerular function.¹⁷ Like ABC, DTG is not recommended in patients with severe hepatic impairment.¹

There is a need for more data and subsequent treatment options for patients living with HIV and ESRD, reducing the need for dosage adjustments and pill burden. Based on known PK properties, ABC/3TC/DTG STR may represent a promising treatment option for these patients who are HLA-B*5701 negative on HD. The objective of this case series was to present the safety and efficacy data of ABC/3TC/DTG STR in patients with HIV and ESRD on HD.

Methods

The protocol (2018-0326) was reviewed by our institution's Office for the Protection of Research Subjects and was determined to not meet the definition of human subjects research. This was a retrospective case series of six patients from two clinical sites within an academic medical center in the Chicagoland area. Patients were included if they were HIV-positive, had a history of ESRD and were maintained on chronic intermittent HD, were receiving the ARV regimen ABC/3TC/DTG STR, and had at least one set of virologic data (HIV-RNA [HIV ribonucleic acid] and CD4 cell count) before and after initiating ABC/3TC/DTG STR. Information was obtained via the electronic medical record (EMR). Data collection points included

demographics, laboratory values, medications, and self-reported adherence and adverse events. HIV-RNA (viral load) was quantified by the TaqMan™ assay with a lower limit of detection of 20 copies/mL. Medication lists were derived from clinician notes and/or the medication/order list in the EMR. Clinician notes were reviewed for the assessment of drug–drug interactions and verified against the US DHHS Guidelines and the University of Liverpool HIV Drug Interactions Website.^{1,18} Our standard of care typically includes documentation of self-reported adherence and adverse events at each clinic visit.

Results

Baseline demographics

Six patients were identified and met inclusion criteria. Baseline demographics are presented in Table 1. Average age (± standard deviation, SD) was 59 ± 8 years. The majority of patients were cis-gender male (5, 83%), non-Hispanic Black (5, 83%), and did not have an acquired immunodeficiency syndrome (AIDS) diagnosis (4, 67%). Median number of years living with HIV and maintained on HD was 21 (range: 5–27) and 7 (range: 1–7) years, respectively. Five patients had a suspected or diagnostically proven renal failure etiology documented in the EMR. HIV was the documented cause of renal failure for two patients, while non-HIV-related for the remainder of patients. All patients were HLA-B*5701 negative.

All patients were on multiple-tablet regimens (MTRs) prior to the initiation of ABC/3TC/DTG STR (“the switch”). Three patients (50%) were on a

protease inhibitor (PI)-based regimen, two (33%) were on an integrase strand transfer inhibitor-based regimen, and one patient was on a non-nucleoside reverse transcriptase inhibitor-based regimen. Prior regimens for all patients included 3TC as part of the nucleoside reverse transcriptase inhibitor (NRTI) backbone. Three patients (50%) were on full-dose ABC/3TC fixed dose combination tablet. The other three patients (50%) were on renally dose-adjusted 3TC; one in combination with ABC, one in combination with renally dose-adjusted tenofovir disoproxil fumarate (TDF), and one in combination with both ABC and renally dose-adjusted TDF.

The majority of patients (5, 83%) were switched to an ARV regimen only consisting of ABC/3TC/DTG STR. Weekly TDF was continued in addition to ABC/3TC/DTG STR for patient one due to the presence of an M184V mutation.

Virologic/immunologic data and adherence

Virologic/immunologic data and self-reported adherence are presented in Table 2. Patients were on ABC/3TC/DTG STR for a mean (±SD) of 11 ± 5 months at the time of the most recent labs. Self-reported adherence was documented for five (83%) patients.

Five patients (83%) achieved undetectable HIV-RNA after the switch while only four patients (46%) were undetectable immediately prior. Patients three, four, and six maintained complete virologic suppression before and after the switch, without evidence of virologic blips. Patients one and two gained virologic suppression after the switch. Patient five lost complete virologic suppression.

Table 1. Baseline demographics.

Patient	Age (yrs)	Sex/gender identity	Race/ethnicity	HIV/AIDS diagnosis date	HD initiation date	Renal failure etiology	ARV regimen before switch	ABC/3TC/DTG-based regimen
1	58	F/F	NH/B	1994/2010	2010	HIV	ABC + ATV/r + 3TC 25 mg oral solution + weekly TDF	ABC/3TC/DTG + weekly TDF
2	48	M/M	Other/H	2009/N/A	2015 (PD prior)	DM	ABC/3TC + ATV/r	ABC/3TC/DTG
3	53	M/M	NH/B	1995/N/A	2010	HIV	ABC/3TC + NVP XR	ABC/3TC/DTG
4	56	M/M	NH/B	1995/1995	NR	NR	ABC/3TC + EFV	ABC/3TC/DTG
5	72	M/M	NH/B	1990/N/A	2017	HTN	ABC + 3TC 100 mg + DTG	ABC/3TC/DTG
6	64	M/M	NH/B	2012/N/A	2010	HTN	3TC 100 mg + BID RAL + weekly TDF	ABC/3TC/DTG

Note: Oral tablet or capsule formulation of medication unless otherwise noted; Doses for ARVs as below unless otherwise noted; ARVs dosed once daily unless otherwise noted.

3TC: lamivudine 300 mg; ABC: abacavir 600 mg; ABC/3TC: abacavir/lamivudine 600/300 mg; ABC/3TC/DTG: abacavir/lamivudine/dolutegravir STR 50/600/300 mg; ATV/r: atazanavir + ritonavir 300/100 mg; DTG: dolutegravir 50 mg; EFV: efavirenz 600 mg; NVP XR: nevirapine XR 400 mg; RAL: raltegravir 400 mg; TDF: tenofovir disoproxil fumarate 300 mg; AIDS: acquired immunodeficiency syndrome; ARV: antiretroviral; B: Black (African-American); BID: twice daily; DM: diabetes mellitus; F: female; H: Hispanic; HIV: human immunodeficiency virus; HIVAN: HIV-associated nephropathy; HD: hemodialysis; HTN: hypertension; M: male; N/A: not applicable; NH: non-Hispanic; NR: not reported; PD: peritoneal dialysis; switch: change from previous regimen to DTG/ABC/3TC STR-based regimen; yrs: years.

Table 2. Virologic/immunologic data, adherence, and adverse events.

Patient	HIV-RNA before switch	Most recent HIV-RNA	HIV-RNA ever detectable after switch?	CD4/% before switch	Most recent CD4/%	Time after switch to most recent labs (mths)	Self-reported ARV adherence after switch	Self-reported adverse events after switch
1	62,478	ND	Yes	93/6	218/21	14	100%	None
2	33	ND	No	975/41	1026/48	18	100%	None
3	ND	ND	No	617/34	524/33	14	100%	Nausea
4	ND	ND	No	454/32	374/26	5	NR	None
5	ND	81	Yes	452/37	400/26	9	3–4 missed doses/mth	None
6	ND	ND	Yes	437/43	423/44	5	100%	None

ARV: antiretroviral; CD4: cluster of differentiation 4 cell, cells/ μ L; HIV: human immunodeficiency virus; HIV-RNA: HIV ribonucleic acid (viral load), copies/mL; mth(s): month(s); ND: non-detectable; NR: not reported; switch: change from previous regimen to DTG/ABC/3TC STR-based regimen.

Patients one and two had detectable viral loads before the switch, with self-reported noncompliance to prior antiretroviral therapy (ART). Patient one reported noncompliance due to pill burden and distaste for 3TC oral solution. Patient two reported noncompliance secondary to diarrhea. After the switch, both patients self-reported 100% adherence and achieved viral suppression. The viral load for patient one achieved near suppression, slightly above the lower limit of detection, for the first ten months after the switch. Viral load for patient two was undetectable at first three-month follow-up and remained undetectable after the switch. Time to complete virologic suppression for patients one and two was ten and three months, respectively.

Patient five was unable to achieve virologic suppression secondary to self-reported nonadherence after the switch. Initially undetectable, with a self-reported 100% adherence on his prior regimen, subsequent viral loads obtained after initiation of ABC/3TC/DTG STR were slightly above the lower limit of detection. Although detectable, his viral load did not meet the definition of virologic failure (i.e. HIV-RNA level greater than 200 copies/mL).¹ This patient subsequently transferred care to another facility and we were unable to obtain additional records.

No decline in immunologic function was noted after the switch (Table 2). The majority of patients (5, 83%) had CD4 cell counts greater than 200 cells/ μ L on prior ART, which was maintained after the switch. The lone patient with a CD4 was less than 200 cells/ μ L did not change after the switch. Of note, even though the CD4 did not rise above 200 cells/ μ L, the CD4 percent increased to 15% two months after the switch and has remained above 14% since. Because of this, the medical team deemed immunologic function to be substantially restored and *Pneumocystis* pneumonia prophylaxis was discontinued.

Adverse events

Only one patient self-reported an adverse event (nausea) after switching (Table 2). Relation of this event to the ABC/3TC/DTG switch was unclear and did not require further work-up per provider judgment. Symptoms did not necessitate a discontinuation of therapy and resolved with a short course of prochlorperazine.

Lactic acid levels are not recommended as standard laboratory monitoring, and therefore were not obtained for any of the six patients. No changes in standard laboratory indices obtained during routine clinical care were observed or attributed to ABC/3TC/DTG by providers for any patient.

Concomitant medications and pill burden

No patients reported receiving concomitant medications known to interact with ABC/3TC/DTG STR other than polyvalent cations (Table 3), which were separated by a minimum of 2 h. The majority of patients (5, 83%) received documented education on the management of this interaction by a physician and/or clinical pharmacist. Including ART, patients were on a median of 10 (range: 7–17) medications after the switch. The switch from prior ART to ABC/3TC/DTG STR reduced the median number of individual ARV medications prescribed by 2 (range: 1–3) and the number of ARV doses required per week by 14 (range: 7–21). The number of doses per week, rather than per day, was calculated because two patients were on weekly TDF.

Discussion

TDF-containing STRs have a CrCl cutoff of 50 mL/min, while the newer TAF-containing STRs have a cutoff CrCl of 30 mL/min.¹ Despite ABC/3TC/DTG having a CrCl cutoff of 50 mL/min,¹ based on 3TC

Table 3. Concomitant medications.

Patient	Concomitant medications
1	Albuterol inh, Calcitriol, Losartan, Renal MVI , Sevelamer
2	Aspirin, Atorvastatin, Carvedilol, Cinacalcet, Insulin glargine inj, Insulin regular inj, Olanzapine
3	Calcium carbonate, Cinacalcet, Depakote, Docusate, Hydroxyzine, Loratadine, Losartan, Minoxidil, Mirtazapine, Nifedipine XL, Omeprazole, Prochlorperazine, Ranitidine, Renal MVI , Simvastatin, Sucroferric oxyhydroxide
4	Acetaminophen with codeine, Atenolol, Atorvastatin, Calcium–vitamin D, Cinacalcet, Diphenhydramine, Docusate, Levothyroxine, Ranitidine, Renal MVI , Sevelamer, Triamcinolone topical
5	Albuterol inh, Allopurinol, Alprazolam, Carvedilol, Ergocalciferol, Ferrous sulfate , Finasteride, Hydralazine, Nifedipine ER
6	Acetaminophen, Amlodipine, Aspirin, Clonidine, Diphenhydramine, Lisinopril, Renal MVI , Sevelamer

Note: Oral tablet or capsule formulation of medication unless otherwise noted; Potential drug–drug interactions between ABC/3TC/DTG STR and concomitant medications in bold.

inh: inhaled; inj: injection; MVI: multivitamin.

dosing, our outcomes appear to demonstrate it may be safe and efficacious in this understudied population. To our knowledge, this is the first real-world report (outside of clinical trials) demonstrating STR usage in a population commonly overwhelmed with numerous medications based on comorbidities.

Impaired renal function is significantly more prevalent in patients living with HIV compared to HIV-negative controls.¹⁹ The incidence of HIV-associated nephropathy (HIVAN) significantly decreased in the highly active antiretroviral therapy era.²⁰ However, other etiologies of chronic renal failure, such as hypertension and diabetes, remain.¹⁹ These factors may be further exacerbated as the HIV population ages. In our population, non-HIV-related renal failure etiologies were more common than HIV-related.

Patients on ESRD require an average of 10–12 medications.²¹ This was similar in our population. Comorbid HIV adds an additional layer of complexity, especially when combination ARVs are divided into individual components to achieve recommended renal dose adjustments. The number of ARV medications prescribed and ARV doses per week decreased when our patients switched to ABC/3TC/DTG STR.

Prevalence rates of medication nonadherence range from 12.5 to 98.6% in patients on HD, with medication-related factors, such as number of prescribed medications and daily tablet count significantly contributing to nonadherence.²² Average rates of nonadherence to ART in patients with HIV range from 50 to 70%.²³ Overall, our population had comparatively high ART adherence.

Data support better ART adherence with STRs compared to MTRs.^{24,25} Switching to ABC/3TC/DTG STR improved adherence and virologic suppression for two of our patients. Conversely, adherence for only one patient decreased after the switch. However, this patient experienced a substantial decline in overall

health around the same time, which could explain his new-onset nonadherence and loss of complete virologic suppression, despite lower ART pill burden. Virologic suppression was maintained for the other three patients. Adherence remained stable for two of these three patients, while adherence was not reported for one patient.

Adverse effects were not observed in previously published PK studies involving HD patients receiving 3TC doses greater than 25 mg daily, despite these patients having much higher AUCs than patients with normal renal function.^{3,4} These studies were admittedly short in duration; however, a previous report of one patient living with HIV on HD receiving 3TC 150 mg twice daily for six months did not demonstrate clinical or biologic adverse events.⁵ Our current report confirms the likelihood of the tolerability of 3TC at the standard dose of 300 mg daily, as contained in ABC/3TC/DTG STR, for up to 18 months in patients living with HIV on HD.

Although not observed in the aforementioned PK studies, lactic acidosis (LA) is a potential complication of 3TC.²⁶ Female gender, obesity, and cumulative NRTI exposure have traditionally been suggested as risk factors.² Additionally, a case–control study of patients living with HIV receiving NRTI therapy with concurrent low CrCl (<70 mL/min) was also found to be a risk factor.²⁶ This finding, especially in the setting of suprathreshold 3TC levels, could be a potential concern for clinicians. However, it is worth noting that seven of the nine subjects experiencing LA in the abovementioned case–control study were on stavudine and/or didanosine at the time of LA diagnosis, which carries the greatest risk of LA among NRTIs.²⁶ No patients in our current report exhibited signs or symptoms concerning for LA, and therefore no lactic acid levels were obtained. To date, a definitive relationship between toxicity and 3TC exposure has not been clearly established.⁸

We acknowledge several limitations of our case series. First, our report is limited to a small number of patients with a narrow duration of follow-up. Second, due to the observational nature of our report, adverse events were limited to self-report and a PK analysis was not conducted. However, we believe self-reported tolerability is a valid and convenient method to determine patient tolerability in the clinical practice setting.

Conclusion

Based on this limited case series, it appears that ABC/3TC/DTG may be a safe and effective ARV STR option for patients with HIV and ESRD on HD. A larger trial including a PK analysis is needed to confirm these findings.

Data sharing

The authors of this paper cannot legally or ethically release the data and other artifacts supporting the results in the paper.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sarah M Michienzi  <http://orcid.org/0000-0003-1182-7997>

References

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Department of Health and Human Services, <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf> (accessed 1 October 2017).
- GlaxoSmithKline. Epivir (lamivudine) (package insert). Research Triangle Park, NC: GlaxoSmithKline, 2016.
- Bohjanen P, Johnson M, Szczech L, et al. Steady-state pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with end-stage renal disease receiving chronic dialysis. *Antimicrob Agents Chemother* 2002; 46: 2387–2392.
- Johnson M, Verpooten G, Daniel M, et al. Single dose pharmacokinetics of lamivudine in subjects with impaired renal function and the effect of haemodialysis. *Br J Clin Pharmacol* 1998; 46: 21–27.
- Izzedine H, Launay-Vacher V and Deray G. Dosage of lamivudine in a haemodialysis patient. *Nephron* 2000; 86: 553.
- Heald A, Hsyu P, Yuen G, et al. Pharmacokinetics of lamivudine in human immunodeficiency virus-infected patients with renal dysfunction. *Antimicrob Agents Chemother* 1996; 40: 1514–1519.
- van Leeuwen R, Lange J, Hussey E, et al. The safety and pharmacokinetics of a reverse transcriptase inhibitor, 3TC, in patients with HIV infection. *AIDS* 1992; 6: 1471–1476.
- Bouazza N, Tréluyer J, Ghosn J, et al. Evaluation of effect of impaired renal function on lamivudine pharmacokinetics. *Br J Clin Pharmacol* 2014; 78: 847–854.
- Chittick G, Gillotin C, McDowell J, et al. Abacavir: absolute bioavailability, bioequivalence of three oral formulations, and effect of food. *Pharmacotherapy* 1999; 19: 932–942.
- Izzedine H, Launay-Vacher V, Aymard G, et al. Pharmacokinetics of Abacavir in HIV-1-infected patients with impaired renal function. *Nephron* 2001; 89: 62–67.
- Yuen G, Weller S and Pakes G. A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; 47: 351–371.
- McDowell J, Chittick G, Ravitch J, et al. Pharmacokinetics of [¹⁴C] abacavir, a human immunodeficiency virus type 1 (HIV-1) reverse transcriptase inhibitor, administered in a single oral dose to HIV-1-infected adults: a mass balance study. *Antimicrob Agents Chemother* 1999; 43: 2855–2861.
- GlaxoSmithKline. Ziagen (abacavir) (package insert). Research Triangle Park, NC: GlaxoSmithKline, 2017.
- Castellino S, Moss L, Wagner D, et al. Metabolism, excretion, and mass balance of the HIV-1 integrase inhibitor dolutegravir in humans. *Antimicrob Agents Chemother* 2013; 57: 3536–3546.
- Moltó J, Graterol F and Miranda C. Removal of dolutegravir by hemodialysis in HIV-infected patients with end-stage renal disease. *Antimicrob Agents Chemother* 2016; 60: 2564–2566.
- Bollen P, Rijnders B, Teulen M, et al. Dolutegravir is not removed during hemodialysis. *AIDS* 2016; 30: 1490–1491.
- GlaxoSmithKline. Tivicay (dolutegravir) (package insert). Research Triangle Park, NC: GlaxoSmithKline, 2017.
- HIV drug interactions. University of Liverpool, www.hiv-druginteractions.org (accessed 1 October 2017).
- Schouten J, Wit F, Stolte I, et al.; The AGEHIV Cohort Study. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals. *Clin Infect Dis* 2014; 59: 1787–1797.
- Razzak Chaudhary S, Workeneh B, Montez-Rath M, et al. Trends in the outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. *Nephrol Dial Transplant* 2015; 30: 1734–1740.

21. Mason N. Polypharmacy and medication-related complications in the chronic kidney disease patient. *Curr Opin Nephrol Hypertens* 2011; 20: 492–497.
22. Ghimire S, Castelino R, Lioufas N, et al. Nonadherence to medication therapy in haemodialysis patients: a systematic review. *PloS One* 2015; 10: e0144119.
23. Chesney M. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis* 2000; 30: S171–S176.
24. Clay P, Nag S, Graham C, et al. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine* 2015; 94: e1677.
25. Yager J, Faragon J, McGuey L, et al. Relationship between single tablet antiretroviral regimen and adherence to antiretroviral and non-antiretroviral medications among veterans' affairs patients with human immunodeficiency virus. *AIDS Patient Care STDS* 2017; 31: 370–376.
26. Bonnet F, Bonarek M, Morlat P, et al. Risk factors for lactic acidosis in HIV-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. *Clin Infect Dis* 2003; 36: 1324–1328.