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Pharmacokinetics of dolutegravir 100 mg once daily with rifampicin

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ABSTRACT

Background: Tuberculosis (TB) causes 25% of all deaths among individuals infected with human immunodeficiency virus (HIV). Rifampicin (RIF) is a potent inducer of drug metabolizing enzymes and drug transporters, and co-administration with dolutegravir (DTG) reduces DTG exposure; this can be overcome by doubling the DTG dose to 50 mg twice daily. This study investigated the effect of RIF on DTG exposure when dosed at 100 mg once daily, which could provide an easier option than 50 mg twice daily.

Methods: An open label, pharmacokinetic (PK) study was undertaken. Healthy HIV-negative subjects received DTG 50 mg for 7 days (PK1), DTG 100 mg for 7 days (PK2), RIF for 14 days, DTG 50 mg + RIF for 7 days (PK3) and DTG 100 mg + RIF for 7 days (PK4). Steady-state full DTG PK profiles were evaluated.

Results: DTG geometric mean ratios (GMRs) of PK3/PK1 of maximum concentration (C_{max}), area under curve (AUC_{24h}) and 24-h post-dose concentration (C_{24h}) were 0.65 [90% confidence interval (CI) 0.55–0.75], 0.44 (90% CI 0.37–0.52) and 0.15 (0.13–90% CI 0.17), respectively. GMRs of PK4/PK1 C_{max}, AUC_{24h} and C_{24h} were 1.09 (90% CI 0.97–1.21), 0.74 (90% CI 0.64–0.86) and 0.24 (90% CI 0.20–0.28), respectively. Median C_{24h} of DTG 50 mg + RIF and DTG 100 mg + RIF were 251 (range 129–706) ng/mL and 140 (range 73–426) ng/mL, respectively.

Conclusion: Although there were substantial reductions in DTG C_{24h} when co-administered with RIF, concentrations of both DTG 50 mg and 100 mg once daily with RIF were still above the protein-binding-adjusted IC_{90} (drug concentration required to inhibit 90% of in-vitro viral replication) of 64 ng/mL. Further studies in HIV-TB co-infected individuals are warranted to confirm these results.

1. Introduction

Co-infection with tuberculosis (TB) and human immunodeficiency virus (HIV) places a tremendous burden on healthcare systems, especially in resource-limited countries. In 2017, the World Health Organization (WHO) estimated that there were 10 million people infected with TB worldwide, and 9% of them were co-infected with HIV. People living with HIV are at 16–27 times higher risk of developing TB than those without HIV infection [1]. The two diseases potentiate one another, increasing the risk of death, treatment failure and relapse [2–4]. It is recommended that antiretroviral therapy (ART) should be initiated soon after the initiation of TB treatment in co-infected individuals [5].

Dolutegravir (DTG) is an integrase strand transfer inhibitor (InSTI) approved for the treatment of HIV-infected naïve and experienced individuals [6–8]. DTG is dosed at 50 mg once daily for ART-naïve and InSTI-naïve patients, and at 50 mg twice daily for patients who harbour InSTI-resistant viruses [9–11]. DTG is a substrate of drug efflux pumps, such as breast cancer resistance protein (BCRP) encoded by *ABCG2*, and P-glycoprotein (P-gp) encoded by *ABCB1*. Once absorbed, DTG is primarily metabolized by uridine 5′-diphospho-glucuronosyltransferase of the 1A1 family (*UGT1A1*), with cytochrome P450 3A4 (*CYP3A4*) as a minor route [9,10].

First-line anti-TB regimen consists of rifampicin (RIF), isoniazid, pyrazinamide and ethambutol. RIF activates pregnane X receptor, consequently inducing the expression of *CYP3A4, UGT1A1, ABCG2* and *ABCB1* [12,13]. Therefore, RIF has potential to lower the concentration of DTG. A phase I, open label, cross-over study in healthy volunteers was conducted to evaluate doubling the dose of DTG to 50 mg twice daily with RIF, which resulted in a modest increase in plasma DTG area under curve (AUC) (33%), maximum concentration (C_{max}) (18%) and 24-h post-dose concentration (C_{24h}) (22%) compared with DTG 50 mg once daily alone, suggesting that DTG 50 mg twice daily with RIF could be used in patients who

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require concomitant treatment for HIV and TB [14]. Interim 24-week analysis from the phase 2 INSPIRING study showed that DTG 50 mg administered twice daily in combination with RIF-based anti-TB treatment was effective and well tolerated in HIV/TB co-infected individuals [15].

However, there are no published data on the exposure of DTG 50 mg once daily or of increased doses once daily with RIF. It is likely that trough concentrations will be significantly lowered by RIF induction, but the inhibitory quotient may still be adequate given that the inhibitory quotient [C_{24h}/drug concentration required to inhibit 90% of in-vitro viral replication (IC_{90})] of DTG 50 mg once daily is 19 [16]. If once-daily doses of DTG achieve adequate concentrations with RIF, this could lead to better virologic outcomes than 50 mg twice daily as it is well established that once-daily HIV/TB treatments are beneficial as they improve adherence [17–19]. This study investigated the exposure of DTG 50 mg and 100 mg once daily with RIF vs. DTG 50 mg and 100 mg alone.

2. Methods

2.1. Study population and design

This open label, sequential pharmacokinetic (PK) study was conducted at St Stephen's Centre in London, UK. Regulatory and ethical approvals (London Riverside Research Ethics Committee) were obtained before initiating the study. Written informed consent was obtained from participants prior to study enrolment. Recruits were healthy HIV-negative males and non-pregnant and non-lactating females aged between 18 and 60 years, with body mass index between 18 and 35 kg/m^2. Eligibility was determined by medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory evaluation. The following exclusion criteria were applied: any clinically significant acute or chronic medical illness, including HIV, hepatitis B and C; evidence of organ dysfunction or abnormal physical examination; vital signs; ECG or clinical laboratory determinations; current or recent (within 3 months) gastrointestinal disease; clinically relevant alcohol or drug use that might adversely affect compliance with trial procedures; use of any other drugs including over-the-counter medications and herbal preparations within 2 weeks of the first dose of study drug; history of allergy to any medications used during the study; and exposure to any investigational drug within 3 months of the first dose of the study drug.

The study duration was 43 days, excluding screening and follow-up. The participants received DTG 50 mg once daily from Day 1 to Day 7, DTG 100 mg once daily from Day 8 to Day 14, RIF 600 mg once daily from Day 15 to Day 28, RIF 600 mg once daily + DTG 50 mg once daily from Day 29 to Day 35, and RIF 600 mg once daily + DTG 100 mg once daily from Day 36 to Day 42. Intensive PK visits were scheduled on Days 7 (PK1), 14 (PK2), 35 (PK3) and 42 (PK4). Blood samples were collected pre-dose, and at 2, 4, 8, 12 and 24 h post-dose. On the intensive PK days, DTG dosing was witnessed following a standard breakfast. RIF was taken on an empty stomach. When RIF and DTG were taken in combination, subjects took RIF on an empty stomach, had breakfast 30 min later and then took their DTG dose. These were also the instructions that subjects received when dosed at home in the morning at the same time every day.

2.2. Collection and quantification of plasma dolutegravir

At each scheduled PK blood draw, approximately 6 mL of whole blood was collected into one 6-mL spray-coated EDTA tube from an indwelling venous catheter or by direct venepuncture. Plasma was obtained after centrifugation of blood samples for 10 min at 2000 *g* at 4 °C, and aliquoted into two Sarstedt storage tubes. Plasma samples were stored at -80 °C before shipping on dry ice to the Jefferiss Trust Laboratory, Imperial College London. DTG plasma concentrations were measured by a validated reverse-phase ultra-high performance liquid chromatography method modified from a previously published method [20]. DTG was measured at a wavelength of 258 nm, and the assay was validated over a calibration range of 50–10 000 ng/mL. The laboratory adhered to the International Inter-laboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma [21].

2.3. Pharmacokinetic and statistical analysis

Given the experience from similar studies conducted previously with DTG [14], within-subject variability [expressed as a coefficient of variation (CV)] of 33% and an expected withdrawal rate of 30%, a sample size of 12 subjects completing the study was considered sufficient to allow relevant conclusions to be drawn. Sixteen subjects were therefore enrolled in the trial, and 14 completed the study. All PK parameters were calculated using non-compartmental modelling techniques (WinNonlin Phoenix Version 7.0; Pharsight, Mountain View, CA, USA) based on plasma DTG concentration–time data, including C_{24h}, C_{max} and AUC_{24h}. Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (CI), were calculated for all parameters. Within-subject changes of drug concentrations (PK2 vs. PK1, PK4 vs. PK3, PK3 vs. PK1, PK4 vs. PK2, PK3 vs. PK1) were evaluated by calculating GM ratios (GMRs) and 90% CI. Individual intervariability in DTG PK parameters was expressed as a percentage CV [(standard deviation/mean) x 100]. Bioavailability was calculated as (AUC of dose 1/AUC of dose 2) * (dose 2/dose1).

3. Results

3.1. Study populations

In total, 16 subjects were screened and enrolled in the study, and 14 completed all PK sampling days. One withdrew consent for personal reasons and one stopped the study at Day 22 while taking RIF alone due to the development of an allergic reaction. The median age was 32 (range 22–55) years and median body mass index was 27 (range 18–32) kg/m^2. Nine (64%) subjects were male, 11 (79%) were White, two were Black Caribbean and one was of Asian origin.

3.2. Dolutegravir pharmacokinetics

The GM plasma concentration–time profiles of DTG alone (50 mg or 100 mg) and with RIF 600 mg are shown in Fig. 1. Steady-state DTG PK parameters are summarized in Table 1 and GMRs are summarized in Table 2.

The changes in PK parameters when DTG was administered at 100 mg once daily compared with 50 mg (PK2/PK1) were assessed. DTG C_{max}, AUC_{24h} and C_{24h} were increased by 70%, 77% and 90%, respectively. The relative bioavailability of DTG 100 mg compared with DTG 50 mg when administered without RIF (PK2/PK1) was assessed, and AUC_{0-24} was 89% and C_{max} was 85%, confirming a less-than-dose-proportional increase in DTG exposure.

3.3. Effect of rifampicin on dolutegravir pharmacokinetics

The effect on RIF on DTG when the DTG dose was doubled from 50 mg to 100 mg (PK4/PK3) was investigated, and C_{max}, AUC_{24h} and C_{24h} increased by 68%, 70% and 60%, respectively. Following the addition of RIF, the relative bioavailability of DTG 100 mg compared with DTG 50 mg did not change compared with the aforementioned values observed in the absence of RIF (AUC_{0-24} of 85%, C_{max} of 84%).

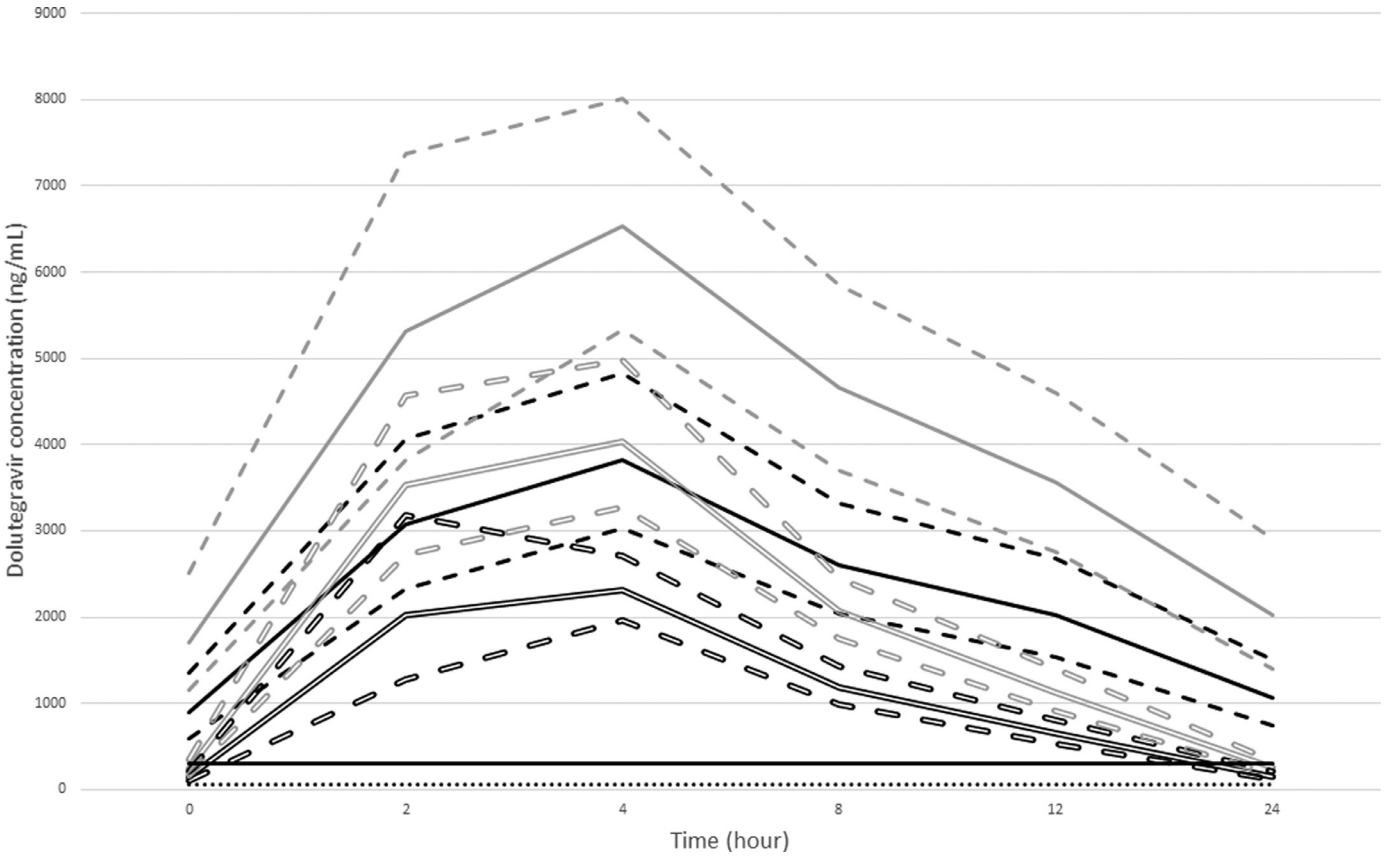

Fig. 1. Geometric mean plasma dolutegravir (DTG) concentration–time curves. DTG 50 mg once-daily (PK1, black solid line), DTG 100 mg once-daily (PK2, grey solid line), DTG 50 mg once-daily plus RIF (PK3, black hollow line), DTG 100 mg once-daily plus RIF (PK4, grey hollow line). Short-dashed lines represent 95% confidence intervals. The black dotted line represents an in-vitro protein-adjusted drug concentration required to inhibit 90% of in-vitro viral replication of 64 ng/mL. The black solid line represents optimal 24-h post-dose concentration derived from an E_{max} model in a phase 2 DTG monotherapy study [21].

Table 1
Summary of steady-state plasma dolutegravir (DTG) pharmacokinetic (PK) parameters following 7 days of administration of DTG 50 mg (PK1), 7 days of administration of DTG 100 mg (PK2), 7 days of co-administration of DTG 50 mg + RIF 600 mg (PK3), and 7 days of co-administration of DTG 100 mg + RIF 600 mg (PK4).

PK parameter	50 mg DTG (PK1)	100 mg DTG (PK2)	50 mg DTG + RIF (PK3)	100 mg DTG + RIF (PK4)
C_{max} (ng/mL)	3969 (3213–4903)	6746 (5571–8169)	2569 (2184–3023)	4312 (3546–5245)
CV%	34	31	28	38
C_{24h} (ng/mL)	1061 (745–1509)	2017 (1401–2904)	156 (115–214)	251 (187–337)
CV%	59	53	60	56
AUC_{24h} (h*ng/mL)	52101 (40195–67534)	92306 (72227–117967)	22750 (19012–27222)	38731 (31867–47073)
CV%	42	39	32	38

C_{max}, maximum concentration; AUC_{24h}, area under the curve; C_{24h}, 24-h post-dose concentration; CV, coefficient of variation.
PK values are provided as geometric mean with 95% confidence interval.

Table 2
Plasma dolutegravir (DTG) pharmacokinetic (PK) parameters following 7 days of administration of DTG 50 mg (PK1), 7 days of administration of DTG 100 mg (PK2), 7 days of co-administration of DTG 50 mg + RIF 600 mg (PK3) and 7 days of co-administration of DTG 100 mg + RIF 600 mg (PK4).

PK parameter	100 mg DTG vs 50 mg DTG (PK2/PK1)	100 mg DTG + RIF vs 50 mg DTG + RIF (PK4/PK3)	50 mg DTG + RIF vs 50 mg DTG (PK3/PK1)	100 mg DTG+ RIF vs 100 mg DTG (PK4/PK2)	100 mg DTG + RIF vs 50 mg DTG (PK4/PK1)
C_{max}	1.70 (1.56–1.85)	1.68 (1.43–1.97)	0.65 (0.55–0.75)	0.64 (0.55–0.74)	1.09 (0.97–1.21)
C_{24h}	1.90 (1.74–2.08)	1.60 (1.40–1.84)	0.15 (0.13–0.17)	0.12 (0.10–0.15)	0.24 (0.20–0.28)
AUC_{24h}	1.77 (1.61–1.94)	1.70 (1.49–1.95)	0.44 (0.37–0.52)	0.42 (0.35–0.50)	0.74 (0.64–0.86)

C_{max}, maximum concentration; AUC_{24h}, area under the curve; C_{24h}, 24-h post-dose concentration.
Values are provided as geometric mean ratio and 90% confidence interval.

As expected, DTG concentrations were reduced when co-administrated with RIF (PK3/PK1, PK4/PK2). Median DTG C_{24h} with RIF for 50 mg and 100 mg daily doses were 140 (range 73–426) ng/mL and 277 (range 129–706) ng/mL, respectively, which are both above the protein-binding-adjusted IC_{90} of 64 ng/mL. RIF induced similar reductions in DTG PK parameters regardless of the dose of DTG. GMRs of PK3/PK1 and PK4/PK2 are similar for C_{max}, AUC_{24h} and C_{24h}. When comparing PK parameters of DTG 100 mg in co-administration with RIF with DTG 50 mg administered alone (PK4/PK1), GMRs of C_{max}, AUC_{24h} and C_{24h} were 1.09 (90% CI 0.97–1.21), 0.74 (90% CI 0.64–0.86) and 0.24 (90% CI 0.20–0.28), respectively.

3.4. Safety and tolerability

Overall, DTG with RIF was well tolerated with no grade 3 or grade 4 or serious adverse events reported. One subject discontinued due to a grade 2 urticarial rash, characteristic of an allergic reaction probably related to RIF, and another withdrew consent for personal reasons.

4. Discussion

RIF, together with isoniazid, is the core of the anti-TB first-line regimen. However, RIF is a potent inducer of metabolizing enzymes and transporters, causing complex PK interactions with co-administered drugs including antiretrovirals, which may undermine drug efficacy and increase the risk of virological failure and drug resistance. This study investigated the PK of DTG 50 mg and 100 mg once daily in the presence and absence of RIF 600 mg in HIV-negative healthy volunteers. The key objective of this phase I study was to compare the PK of DTG 100 mg once daily in the presence of RIF with DTG 50 mg once daily without RIF, as DTG 100 mg once daily with RIF to treat HIV patients co-infected with TB is more desirable than DTG 50 mg twice daily with RIF in resource-limited settings.

Three PK parameters (C_{max}, AUC_{24h} and C_{24h}) were used to evaluate the effect of RIF on DTG at steady state. Dose-proportional increases in plasma exposure (AUC_{24h}) were linear when increased from 25 mg DTG to 50 mg DTG in a previous trial [22]. However, in the present study, DTG AUC_{24h} was increased in a less-than-dose-proportional manner (by 77%) when the dose of DTG (without RIF co-administration) increased from 50 mg to 100 mg, which indicates that drug absorption reached saturation in the range of 50–100 mg DTG. DTG AUC_{24h} was increased to a similar extent (70%) when the dosage of DTG was doubled in the presence of RIF, which suggests that RIF has no additional effect on the saturation limit of DTG absorption.

An E_{max} model developed in a phase 2 DTG monotherapy study demonstrated that DTG efficacy was optimal when C_{24h} was >300 ng/mL [23]. In the present study, RIF significantly reduced DTG 100 mg once daily C_{24h} by 76% and 50 mg once daily by 85% compared with 50 mg DTG once daily alone. This reduction of C_{24h} suggests that RIF has a great influence on hepatic clearance of DTG, likely by inducing the activity of *UGT1A1* and *CYP3A4*. In particular, out of 14 subjects who were given 100 mg DTG with RIF, only five achieved C_{24h} >300 ng/mL. However, it is crucial to highlight that DTG C_{24h} measured in all study subjects during RIF intake remained 2–14 fold above the in-vitro, protein-adjusted IC_{90} of 64 ng/mL [23]. The in-vivo-generated effective concentrations might be more relevant to clinical practice than in-vitro IC concentrations. However, it should be noted that the effective concentrations are derived from monotherapy studies, and no exposure–response relationship was shown in the subsequent phase 2 study when DTG was combined with dual nucleoside reverse transcriptase inhibitors [16]. Therefore, the effective concentrations may differ with combination therapy [24].

Interestingly, the GMR of DTG C_{max} for PK3/PK1 and PK4/PK2 were decreased by only 35% and 36%, respectively; this is a lower reduction compared with AUC_{0-24} and C_{24h}, suggesting that RIF has a limited role in reducing the absorption of DTG by induction of P-gp and BCRP, and it is mainly involved in the induction of DTG clearance. The effect of RIF on DTG PK parameters was compared with another phase 1 study looking at 50 mg DTG twice daily in the presence and absence of RIF [14]. There was a smaller decrease in C_{max} and AUC_{24h} in the presence of RIF in the present study. The discrepancies may originate from whether DTG was administered in the fasted state or with a meal. Food has been shown to increase DTG plasma exposure and reduce the rate of absorption as food contributes to the solubilization of DTG. When administered with low-, moderate- or high-fat meals, compared with fasting, the AUC from 0 h to infinity ($AUC_{0-\infty}$) increased by 33%, 41% and 66%, respectively, and C_{max} increased by 46%, 53% and 67%, respectively. Moreover, DTG is absorbed rapidly, with an observed T_{max} of 2 h in the fasted state, prolonged to 3, 4 and 5 h with low-, moderate- and high-fat meals, respectively [25]. In the present study, patients were instructed to dose DTG after a standardized meal in order to maximize DTG exposure with 20 g of fat content. However, DTG GM C_{24h} when DTG was administered 50 mg twice daily with RIF was 670 ng/mL (CV 55%) [14], which is higher than C_{24h} of 156 ng/mL (CV 60%) and 251 ng/mL (CV 56%) when dosed at 50 mg and 100 mg once daily with RIF, respectively. Importantly, the present study was conducted in healthy volunteers who received a witnessed dose of DTG with food. In real-world settings where drugs may be taken in a fasted state and not always at the same time, interindividual variability may be wider with a higher number of subjects showing concentrations lower than the in-vivo established cut-off.

Ideally, drug–drug interactions with RIF should be done at maximum induction. Maximum induction of CYP3A4 occurs at approximately 2 weeks [26], and RIF auto-induction is 90% maximal at 2 weeks [27]. In the present study, subjects were exposed to 2 weeks of RIF alone before starting the co-administration of DTG, and were subsequently assessed for DTG PK parameters after 3 (PK3) and 4 (PK4) weeks of RIF intake. GMRs of PK3/PK1 and PK4/PK2 were similar for C_{max}, AUC_{24h} and C_{24h} (0.65 vs. 0.64, 0.15 vs. 0.12, 0.44 vs. 0.42, respectively), suggesting that RIF induction had already reached steady state (i.e. maximum) at 3 weeks.

5. Conclusion

DTG C_{24h} was reduced by 76% when dosed at 100 mg with RIF compared with 50 mg DTG once daily alone. This study enrolled a relatively small sample of healthy volunteers in a highly-monitored environment. In real-world settings, it is not always possible to guarantee patients' optimal adherence to medications and their intake with food, with possible consequent reduction in DTG exposure. Nonetheless, considering that concentrations of DTG 100 mg once daily with RIF were all above the protein-binding-adjusted IC_{90} of 64 ng/mL, the results of this study open the possibility of testing this regimen in further trials enrolling people living with HIV undergoing RIF-containing TB treatment. However, in the presence of subjects displaying integrase resistance, doses of DTG 100mg administered once daily may result in insufficient DTG exposure. In conclusion, given the potential benefits of improved adherence to once-daily drug combinations, DTG 100 mg once daily with RIF may present an option for patients who require co-management of HIV and TB. Further studies in people living with HIV with TB are warranted before introducing this strategy into clinical practice.

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Competing interests

Marta Boffito has received travel and research grants from and has been an advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla and Teva. Maddalena Cerrone has received a travel grant from Gilead. Xinzhu Wang, Nadia Castrillo, Francesca Ferretti, Gary Maartens and Myra McClure report no conflicts of interest.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants in this study.

References

[1] World Health Organization. Tuberculosis and HIV. Geneva: WHO; 2018.
[2] Amante TD, Ahemed TA. Risk factors for unsuccessful tuberculosis treatment outcome (failure, default and death) in public health institutions, Eastern Ethiopia. Pan Afr Med J 2015;20:247.
[3] von Braun A, Sekaggya-Wiltshire C, Scherrer AU, Magambo B, Kambugu A, Fehr J, et al. Early virological failure and HIV drug resistance in Ugandan adults co-infected with tuberculosis. AIDS Res Ther 2017;14:1.
[4] Rajesh L, Karunaianantham R, Narayanan PR, Swaminathan S. Antiretroviral drug-resistant mutations at baseline and at time of failure of antiretroviral therapy in HIV type 1-coinfected TB patients. AIDS Res Hum Retroviruses 2009;25:1179–85.
[5] Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray AL, et al. Integration of antiretroviral therapy with tuberculosis treatment. N Engl J Med 2011;365:1492–501.
[6] Cottrell ML, Hadzic T, Kashuba ADM. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. Clin Pharmacokinet 2013;52:981–94.
[7] Das S, Taha H, Das A. Clinical effectiveness of dolutegravir in the treatment of HIV/AIDS. Infect Drug Resist 2015;8:339.
[8] Elliot E, Chirwa M, Boffito M. How recent findings on the pharmacokinetics and pharmacodynamics of integrase inhibitors can inform clinical use. Curr Opin Infect Dis 2017;30:58–73.
[9] Raffi F, Rachlis A, Stellbrink H-J, Hardy WD, Torti C, Orkin C, et al. Once–daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet (London, England) 2013;381:735–43.
[10] Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013;369:1807–18.
[11] Molina J-M, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc 2014;17:19490.
[12] Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Ann Clin Microbiol Antimicrob 2006;5:3.
[13] Albermann N, Schmitz-Winnenthal FH, Z'graggen K, Volk C, Hoffmann MM, Haefeli WE, et al. Expression of the drug transporters MDR1/ABCB1, MRP1/ABCC1, MRP2/ABCC2, BCRP/ABCG2, and PXR in peripheral blood mononuclear cells and their relationship with the expression in intestine and liver. Biochem Pharmacol 2005;70:949–58.
[14] Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr 2013;62:21–7.
[15] INSPIRING: safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 24. CROI 2018, Boston, 4–7 March 2018.
[16] van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012;12:111–18.
[17] Bloom BS. Daily regimen and compliance with treatment. BMJ 2001;323:647.
[18] Parienti J-J, Bangsberg DR, Verdon R, Gardner EM. Better adherence with once–daily antiretroviral regimens: a meta-analysis. Clin Infect Dis 2009;48:484–92.
[19] Maartens G, Boffito M, Flexner CW. Compatibility of next-generation first-line antiretrovirals with rifampicin-based antituberculosis therapy in resource limited settings. Curr Opin HIV AIDS 2017;12:355–8.
[20] Wang X, Penchala SD, Amara A, Else L, Mcclure M, Boffito M. A validated method for quantification of dolutegravir using ultra performance liquid chromatography coupled with UV detection. Ther Drug Monit 2016;38:327–31.
[21] Burger D, Teulen M, Eerland J, Harteveld A, Aarnoutse R, Touw D. The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma: a global proficiency testing program. Ther Drug Monit 2011;33:1.
[22] Min S, Song I, Borland J, Chen S, Lou Y, Fujiwara T, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. Antimicrob Agents Chemother 2010;54:254–8.
[23] Min S, Sloan L, Dejesus E, Hawkins T, McCurdy L, Song I, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS 2011;25:1737–45.
[24] Montaner J, Hill A, Acosta E. Practical implications for the interpretation of minimum plasma concentration/inhibitory concentration ratios. Lancet 2001;357:1438–40.
[25] Song I, Borland J, Chen S, Patel P, Wajima T, Peppercorn A, et al. Effect of food on the pharmacokinetics of the integrase inhibitor dolutegravir. Antimicrob Agents Chemother 2012;56:1627–9.
[26] Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin. Clin Pharmacokinet 2003;42:819–50.
[27] Chirehwa MT, Rustomjee R, Mthiyane T, Onyebujoh P, Smith P, McIlleron H, et al. Model-based evaluation of higher doses of rifampin using a semimechanistic model incorporating autoinduction and saturation of hepatic extraction. Antimicrob Agents Chemother 2016;60:487–94.