Pharmacokinetics of dolutegravir with and without darunavir/cobicistat in healthy volunteers.

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ABSTRACT

Introduction

Dolutegravir (DTG) combined with darunavir/cobicistat (DRV/COBI) is a promising NRTI sparing and/or salvage strategy for the treatment of HIV-1 infection.

Methods

This phase 1, open label, 57 day, cross over, pharmacokinetic (PK) study, enrolled healthy volunteers aged 18-65 years, who were randomized to one of two groups. Group one received DTG 50mg once daily (OD) D for 14 days followed by a 7 day wash out, a 14 day DTG/DRV/COBI OD co-administration period followed by a 7 day wash out and finally a 14 day period of DRV/COBI 800/150mg OD. Group 2 followed the same sequence starting with DRV/COBI and concluding with DTG. Each group underwent intensive PK sampling over 24hrs on day 14 of each drug period and DTG/DRV/COBI concentrations were measured by validated LC-MS/MS methods.

Results

Twenty participants completed all PK phases. Thirteen were female and median age and BMI were 33.5yrs and 27kg/m^2. DTG geometric mean ratios (GMR, DTG+DRV/COBI *versus* DTG alone) and 90% confidence intervals (CI) for C_{max}, AUC_{0-24} and C_{24h} were 1.01 (0.92-1.11), 0.95 (0.87-1.04) and 0.9 (0.8-1.0). DRV GMR (DRV/COBI+DTG versus DRV/COBI alone) and 90%CI for $C_{max,}$ AUC_{0-24} and C_{24h} were 0.90 (0.83-0.98), 0.93 (0.86-1.00) and 0.93 (0.78-1.11). No grade 3 or 4 adverse events or laboratory abnormalities were observed.

Conclusions

Concentrations of DTG during co-administration with DRV/COBI decreased by 10% or less and those of DRV remained unchanged suggesting this combination can be

prescribed safely in the treatment of HIV-1 at standard doses, including in patients harbouring resistance that benefit from optimal antiretroviral exposures.

INTRODUCTION

Triple-drug antiretroviral (ARV) therapy has been the cornerstone of HIV treatment since 1996, leading to unprecedented success in disease control in people living with HIV (PLWH). With increasingly potent agents, there has, in recent years, been a drive to investigate treatment simplification strategies that aim to lessen toxicity, drug interactions and cost through reducing the number of drugs taken. [1] Current available evidence favours dual therapy over monotherapy and is most reasuring in suppressed patients who have maintained virological suppression for at least six months on triple therapy. [2]

Dolutegravir (DTG) and boosted darunavir (DRV/b) are both strong players in this paradigm shift, featuring individually in most of the recent dual combinations studied [2]. They are the agents with the highest potency and resistance barrier within their respective classes and overall [3, 4] and are therefore also important to salvage therapy in patients experiencing treatment failure and harbouring multi-class drug resistances. [5, 6] DTG and DRV/ritonavir (RTV) have individually been paired with lamivudine (3TC) in dual therapy studies, with promising data in treatment naïve and in virologically suppressed patients. [7-12] DTG combined with rilpivirine (RPV) has also been studied in a large randomized, open-label, phase III trial (SWORD 1&2) and in smaller cohort studies, [13-15] showing high efficacy and cost savings [16] when used as maintenance therapy (albeit with slightly higher discontinuation rates secondary to AEs compared to a control standard treatment arm (3% *versus* 1%)).

However, these options are not appropriate in the context of NRTI-related long-term toxicities and/or NRTI/NNRTI-associated resistance mutations. [17] As an NRTI/NNRTI-sparing strategy, the combination of DTG and DRV/b can play a key role in this setting

especially that both agents have a high affinity for their target enzymes [18, 19] and together offer convenience, simplicity, potency and a high genetic barrier. [20]

Two cohort studies have been published on the use of DTG/DRV/RTV in difficult to treat patients. [21, 22] In Canada, Wheeler et al demonstrated maintenance of viral suppression at 12 months and high tolerability in 13 HIV patients with primary transmitted thymidine analogue mutation (TAM) resistance, who switched from a complex salvage multi-drug regimen to DTG/DRV/RTV. [21] Similarly, in Italy, Capetti et al followed 130 patients, with a current or past history of virological failure and documented viral resistance to one to five ARVs, who switched to DTG/DRV/RTV for simplification or rescue therapy. At the 48-week follow up, subjects with active HIV replication dropped from 40% at baseline to 6.1% and the metabolic impact was favourable. [22] A single-point pharmacokinetic (PK) analysis in a subgroup of this study (32 subjects) confirmed adequate median minimum concentrations (C_{24h}) for both drugs (DTG 579 ng/mL; DRV 3007 ng/mL). The DUALIS study is a large, prospective, interventional, randomized, controlled study set up to assess the safety and efficacy of a once-daily (OD) DTG with DRV/RTV OD maintenance therapy. Whilst, recruitment is ongoing, an intensive PK sub-study over 12 hours has been published and describes all steady-state PK parameters for both drugs during co-administration (median maximum concentration (C_{max}) were 3427 ng/mL for DTG and 6170 ng/mL for DRV, C_{12h} 637 ng/mL for DTG and 1245 ng/mL for DRV and area under the curve (AUC_{0-12}) were 26809 ng*h/mL for DTG and 49920 ng*h/mL for DRV), C_{24h} was not measured. [23]

PK data for DTG coadministration with DRV/cobicistat (COBI) are, however, very limited to date. COBI [24] is a newer, approved alternative pharmacological booster to RTV, which may be preferable in some patients. It has a lower potential for drug interactions than RTV, due to its more selective inhibition of CYP3A and lower likelihood for enzymatic

induction. [25] DTG C_{24h} doubled, when measured at least 10 days after switching from DRV/RTV to DRV/COBI in a therapeutic drug monitoring (TDM) survey of HIV infected subjects (n=12), [26] in contrast to a 38% decrease seen with DRV/RTV twice daily in healthy volunteers [27].

No intensive PK data have been published to date on DTG/DRV/COBI co-administration. We, therefore, aimed to describe the steady-state PK of DTG 50 mg (Tivicay®) once daily (OD) and of fixed dose DRV/COBI 800/150 mg (Rezolsta®) OD, over 24 hours when co-administered in healthy volunteers.

METHODS

Participants

Eligible participants were male and non-pregnant and non-lactating female healthy volunteers aged between 18 and 65 years with a BMI between 18 and 35 kg/m^2. Participants were excluded if they had any significant acute or chronic medical illness; abnormal physical examination, ECG or clinical laboratory determinations; positive screens for HIV, hepatitis B or C; current or recent (within three months) gastrointestinal disease; clinically relevant alcohol or drug use that the investigator felt would adversely affect compliance with trial procedures; exposure to any investigational drug or placebo within three months of the first dose of the study drug; use of any other drugs, including over the counter medications and herbal preparations, within two weeks of the first dose of the study drug; and previous allergy to any of the constituents of the pharmaceuticals administered during the trial.

Study design

The study design is illustrated in figure 1. This was a phase 1, open label, 57 day, crossover PK study carried out at the Clinical Trial Unit of the St. Stephen's Centre, Chelsea, and Westminster Hospital, London, United Kingdom.

At screening, participants had a clinical assessment and routine laboratory investigations performed. After successful screening, eligible participants were randomized to one of two groups. Group one received DTG 50 mg OD for 14 days followed by a 7 day wash out (day 15 – 21). From day 22 to 35, in the coadministration period, they received DTG 50 mg OD plus DRV/COBI 800/150 mg OD for 14 days, which was followed by a 7 day wash out (day 36 – 42) and finally a 14 day period of DRV/COBI 800/150 mg OD ensued. Group 2 followed the same structured sequence but started with DRV/COBI 800/150 mg OD and concluded with DTG 50 mg OD. The safety and tolerability of study medications were evaluated throughout the trial (on days 7, 28, 49, PK days and at follow-up) using the NIAID Division of AIDS table for grading the severity of adult and pediatric adverse events to characterize abnormal findings, vital signs, physical examinations and clinical laboratory investigation (published 2004). Each group underwent intensive PK sampling on study days 14, 35 and 56 to measure plasma concentrations of DTG and/or DRV/COBI at 0 (pre-dose), 2, 4, 8, 12 and 24 hours post dose. On the PK days, study staff witnessed study medication intake with a standardized breakfast (626 kcal) and 240 mL of water.

Analytical and PK methods

Blood samples were collected into lithium heparin-containing blood tubes (12 mL) at each time-point, immediately inverted several times and then kept on ice or refrigerated until centrifugation. Within 30 minutes of blood collection, each blood sample was centrifuged for 10 min at 2000 g at 4C. Plasma was then aliquoted equally into three 2.0

mL tubes (Sarstedt, Germany) and stored at -20C.

Samples were shipped on dry ice to the Liverpool Bioanalytical Facility for analysis. The laboratory is Good Clinical Laboratory Practice-accredited and participates in an external quality assurance scheme (KKGT, the Netherlands).

Quantification of dolutegravir, darunavir, and cobicistat

Concentrations of DTG, DRV and COBI in plasma were measured using validated high-pressure liquid chromatography–tandem mass spectrometry methods as previously described (HPLC MS/MS). [28, 29] The lower limits of quantification (LLQ) for plasma DTG was 0.75 ng/mL, 15 ng/mL for DRV and 10 ng/mL for COBI. For concentrations below the assay limit of quantification, a value of one-half of the quantification limit was used. Accuracy (percentage bias) was between 98.0% and 104.6% (DTG) 94.2% and 101.2% (DRV) and 92.3% and 104.0% (COBI), and precision was between 4.6% and 6.2% (DTG), 4.4% and 6.0% (DRV) and 3.1% and 6.5% (COBI).

Data analysis

The calculated PK parameters for plasma DTG, DRV and COBI were C_{24h}, C_{max} and AUC from 0 to 24 hours ($AUC_{0–24}$). All PK parameters were calculated using actual blood sampling time and non-compartmental modeling techniques (WinNonlin Phoenix, version 6.1; Pharsight, Mountain View, CA). Descriptive statistics, including geometric mean (GM) and 95% confidence intervals (95% CI) were calculated for DTG, DRV and COBI plasma PK parameters. Each drug PK parameter during the co-administration period was compared to the unaccompanied drug PK parameter by calculating GM ratios (GMR) and 90% CI (co-administered/alone).

Inter-individual variability in drug PK parameters was expressed as a percentage

coefficient of variation [CV, (standard deviation/mean)×100].

Since both COBI and DTG are associated with a small rise in creatinine through MATE1 and OCT2 inhibition respectively, we evaluated the statistical significance of the changes in creatinine from baseline using the two-sided Wilcoxon signed-rank test for paired samples.

Statistical power

This is an exploratory study and, as such, no formal sample size calculation was performed. Twenty (20) participants completing the study was deemed appropriate to allow for relevant conclusions, as is standard for PK studies.

Ethics

The study protocol was approved by the Surrey Borders Research Ethics Committee and by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki (NCT03094507).

RESULTS

Study Population

Twenty-five healthy volunteers were screened, 21 attended baseline and 20 completed all PK phases (eleven in group 1 and 9 in group 2; one subject withdrew for personal reasons). Median age was 33.5 years (range 24-63), 13 participants were female and median body mass index (BMI) was 27 (range 20-31) kg/m^2. Thirteen subjects described themselves as Caucasian, six as Black African/Caribbean and one as White and African.

DTG, DRV and COBI plasma pharmacokinetics

Table 1 summarizes the PK parameters of DTG and DRV/COBI when administered alone or together in the co-administration phase, in both groups combined.

Dolutegravir plasma pharmacokinetics

Figure 2 illustrates the DTG GM plasma concentration *versus* time curves with and without DRV/COBI, in relation to DTG's protein adjusted (PA) 90% inhibitory concentration (IC_{90}) for wild type virus (64 ng/mL). [30] DTG geometric mean ratios (GMR, DTG+DRV/COBI *versus* DTG alone) and 90% confidence intervals (CI) for C_{max}, AUC_{0-24} and C_{24h} were 1.01 (0.92-1.11), 0.95 (0.87-1.04) and 0.9 (0.8-1.0). No differences were seen between group 1 and 2.

The inter-individual variability in DTG values was between 23 and 40% when administered alone and between 28 and 48% during co-administration with DRV/COBI.

Darunavir plasma pharmacokinetics

Figure 3 shows the DRV GM plasma concentration *versus* time curves with and without DTG in relation to DRV's PA-IC_{90} (200 ng/mL). [31] DRV GMR (DRV/COBI+DTG versus DRV/COBI alone) and 90% CI for C_{max}, AUC_{0-24} and C_{24h} were 0.90 (0.83-0.98), 0.93 (0.86-1.00) and 0.93 (0.78-1.11) and for COBI C_{max}, AUC_{0-24} and C_{24h} were 0.96 (0.89-1.04), 0.98 (0.88-1.08) and 0.98 (0.79-1.22). The inter-individual variability in DRV values was between 31 and 52% when administered alone and between 20 and 53% during co-administration with DTG.

C_{24h} remained seven to 32 fold above the PA-IC_{90} (64 ng/mL) [30] for DTG and one and a half to 11 fold above the PA-IC_{90} (200 ng/mL) [31] for DRV in all subjects (except for one participant with a DRV C_{12h} of 1428 ng/mL but C_{24h} 185 ng/mL).

Safety and tolerability

The studied drugs were well tolerated, with no grade 3 or 4 side effects or laboratory abnormalities. Median (IQR) creatinine at baseline was 67 µmol/L (63-71), during DRV/COBI adminstration 70 µmol/L (65-74), during DTG adminstration 76 µmol/L (69-81) and during coadministration 74.5 µmol/L (70-79.5). The difference between baseline and during co-administration was significant (T=2.5, p<0.01), which was driven by DTG. However, adding DRV/RTV to DTG did not change creatinine significantly (P>0.05), whilst adding DTG to DRV/RTV did (T=29.5, p<0.01).

DISCUSSION

We characterised the steady state PK of standard dose DTG co-administered with DRV/COBI over 24 hours in healthy volunteers. The changes in DTG PK parameters during co-administration compared to DTG administered alone were minimal. DTG C_{24h} decreased by 10%, whilst AUC decreased by 5% and C_{max} remained unchanged. DRV concentrations also decreased by less than 10%. DTG and DRV concentrations remained manifold above the PA-IC_{90} for wild type virus in all participants at all time points, suggesting that the combination of DTG and DRV/COBI can be prescribed safely in the treatment of HIV-1, including in patients harbouring resistance that benefit from optimal antiretroviral exposures. In contrast, DTG C_{24h} had decreased by 38% when co-administered with DRV/RTV (twice daily) in early DTG drug interaction studies, which was not deemed clinically significant (C_{max} decreased by 11% and AUC 22%; participants received multi-dose DTG 30 mg, administered with food). [27]

Our findings are in agreement with Gervasoni *et al.*, who showed a doubling of DTG C_{24h} in HIV patients who switched from DRV/RTV to DRV/COBI. [26] DTG is primarily metabolised by UDP-glucuronosyltransferase-1A1 (UGT1A1) and is only a minor substrate for cytochrome P450 (CYP) 3A4. [32] Whilst both COBI and RTV are potent CYP3A4 inhibitors, unlike RTV, COBI does not induce glucoronidation (or any CYP enzymes), [33] which is likely to explain the difference in effect on DTG PK seen between the two pharmacological boosters. Interestingly, Gervasoni *et al.* commented on the possibility that their observed PK interaction between DTG and the boosting agents may be driven at least in part by increased DTG absorption mediated by a higher degree of inhibition of COBI on intestinal efflux transporters (P-Glycoprotein, PGP, and Breast Cancer Resistant Protein, BCRP), of which DTG is a know substrate. [26, 33] As no rise in DTG C_{max} was seen in our study, our results would suggest the inhibitory effect of COBI on these transporters is only a limited *in vivo*, at least in the context of DRV.

DTG does not induce or inhibit CYP enzymes, therefore effects on DRV and COBI (which are mainly metabolized by CYP3A4) were not expected during coadministration with DTG.

Interestingly, the PK parameters of DTG in our study were, overall, lower than seen in Min *et al.*'s study (also healthy volunteers, n=8, food intake not specified) when administered alone and lower than in the Gervasoni *et al*. study when co-administered with COBI, highlighting the importance of describing intra-individual effect in drug interaction studies.

Serum creatinine concentrations significantly increased from baseline during DTG administration, but no significant increment was recorded when DRV/COBI was added

to DTG, which is consistent with previous observations that administration may not result in additive renal toxicity at least in the short-term. [26, 34]

There are limitations in our study. Subjects were healthy volunteers and conclusions cannot be fully drawn in HIV infected participants. In licencing trials, DTG concentrations appeared generally lower in HIV infected participants than in healthy volunteers. [30] Indeed, discrepancies in antiretroviral drug PK between healthy volunteers and people living with HIV have been previously described (particularly for the protease inhibitors to date). [35] It thought such differences are related to physiological variability in several parameters between the two populations, including enzyme activity and a-1-acid glycoprotein expression. [35] Similarly, pharmacodynamics deductions cannot be drawn; however, previous cohort studies have reported good efficacy of DTG/DRV/COBI in small groups of HIV infected subjects.

The strengths of our study lie in its prospective, controlled and crossover design, which allowed an analysis of *intra-individual* effect. Additionally the study population was appropriately diverse in gender, ethnicity and age.

In conclusion, we investigated the intra-individual variance in DTG and DRV/COBI PK parameters when they are administered together compared to alone. Our results suggest that no dose adjustment is required in either agents and that this combination can be prescribed safely in the treatment of HIV-1, including in patients harbouring resistance.

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CONTRIBUTIONS

EE wrote the manuscript etc

TRANSPARENCY DECLARATIONS

ERE: has received speaking and travel grants from Janssen, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, and Gilead.

MC

LE

AA

EB

SK has received research support from ViiV, Gilead, Merck, Janssen, and honoraria from ViiV, Merck and Gilead.

AO

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REFERENCES

1. Baril JG, Angel JB, Gill MJ *et al.* Dual Therapy Treatment Strategies for the Management of Patients Infected with HIV: A Systematic Review of Current Evidence in ARV-Naive or ARV-Experienced, Virologically Suppressed Patients. *PLoS One* 2016; **11**: e0148231.
2. de Miguel Buckley R, Montejano R, Stella-Ascariz N *et al.* New Strategies of ARV: the Road to Simplification. *Curr HIV/AIDS Rep* 2018; **15**: 11-9.
3. Arasteh K, Yeni P, Pozniak A *et al.* Efficacy and safety of darunavir/ritonavir in treatment-experienced HIV type-1 patients in the POWER 1, 2 and 3 trials at week 96. *Antivir Ther* 2009; **14**: 859-64.
4. Elliot E, Amara A, Jackson A *et al.* Dolutegravir and elvitegravir plasma concentrations following cessation of drug intake. *J Antimicrob Chemother* 2016; **71**: 1031-6.
5. Tashima KT, Mollan KR, Na L *et al.* Regimen selection in the OPTIONS trial of HIV salvage therapy: drug resistance, prior therapy, and race-ethnicity determine the degree of regimen complexity. *HIV Clin Trials* 2015; **16**: 147-56.
6. Castagna A, Maggiolo F, Penco G *et al.* Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. *J Infect Dis* 2014; **210**: 354-62.
7. Pulido F, Ribera E, Lagarde M *et al.* Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. *Clin Infect Dis* 2017; **65**: 2112-8.
8. Sued O FM, Gun A, Belloso W, Cecchini D, Lopardo G. Dual therapy with darunavir/ritonavir plus lamivudine for HIV-1 treatment initiation: week 24 results of the randomized ANDES study. 9th International AIDS Society (IAS) Conference on HIV Science (IAS 2017). Paris, 23–26th July 2017. Oral Abstract MOAB0106LB.
9. Joly V BC, Landman R, Raffi F, Katlama C, Cabié A, *et a*l. Promising results of dolutegravir + lamivudine maintenance in ANRS 167 LAMIDOL trial. Conference on Retroviruses and Opportunistic Infections; February 13–16, 2017; Seattle. Abstract 458.
10. Cahn P, Rolon MJ, Figueroa MI *et al.* Dolutegravir-lamivudine as initial therapy in HIV-1 infected, ARV-naive patients, 48-week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. *J Int AIDS Soc* 2017; **20**: 21678.
11. Taiwo BO ZL, Nyaku AN, Stefanescu A, Sax PE, Haas D et al. ACTG A5353: a pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA < 500,000 copies/mL. 9th International AIDS Society (IAS) Conference on HIV Science (IAS 2017). Paris, 23–26th July 2017. Oral Abstract MOAB0107LB.
12. Taiwo BO, Marconi VC, Berzins B *et al.* Dolutegravir plus lamivudine maintain HIV-1 suppression through week 48 in a pilot randomized trial. *Clin Infect Dis* 2017.
13. Llibre JM, Hung CC, Brinson C *et al.* Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018; **391**: 839-49.
14. Gantner P, Cuzin L, Allavena C *et al.* Efficacy and safety of dolutegravir and rilpivirine dual therapy as a simplification strategy: a cohort study. *HIV Med* 2017; **18**: 704-8.

15. Capetti AF, Cossu MV, Paladini L *et al.* Dolutegravir plus rilpivirine dual therapy in treating HIV-1 infection. *Expert Opin Pharmacother* 2018; **19**: 65-77.
16. Girouard MP, Sax PE, Parker RA *et al.* The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of HIV Infection in the United States. *Clin Infect Dis* 2016; **62**: 784-91.
17. Pasquau J, Hidalgo-Tenorio C. Nuke-Sparing Regimens for the Long-Term Care of HIV Infection. *AIDS Rev* 2015; **17**: 220-30.
18. Dierynck I, De Wit M, Gustin E *et al.* Binding kinetics of darunavir to human immunodeficiency virus type 1 protease explain the potent antiviral activity and high genetic barrier. *J Virol* 2007; **81**: 13845-51.
19. Hightower KE, Wang R, Deanda F *et al.* Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. *Antimicrob Agents Chemother* 2011; **55**: 4552-9.
20. Capetti AF, Sterrantino G, Cossu MV *et al.* Salvage therapy or simplification of salvage regimens with dolutegravir plus ritonavir-boosted darunavir dual therapy in highly cART-experienced subjects: an Italian cohort. *Antivir Ther* 2017; **22**: 257-62.
21. Wheeler J, Chan S, Harrigan PR *et al.* Dolutegravir with boosted darunavir treatment simplification for the transmitted HIV thymidine analog resistance in Manitoba, Canada. *Int J STD AIDS* 2018; **29**: 520-2.
22. Capetti AF, Cossu MV, Orofino G *et al.* A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. *BMC Infect Dis* 2017; **17**: 658.
23. Spinner CD, Kummerle T, Krznaric I *et al.* Pharmacokinetics of once-daily dolutegravir and ritonavir-boosted darunavir in HIV patients: the DUALIS study. *J Antimicrob Chemother* 2017; **72**: 2679-81.
24. Deeks ED. Cobicistat: a review of its use as a pharmacokinetic enhancer of atazanavir and darunavir in patients with HIV-1 infection. *Drugs* 2014; **74**: 195-206.
25. Marzolini C, Gibbons S, Khoo S *et al.* Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother* 2016; **71**: 1755-8.
26. Gervasoni C, Riva A, Cozzi V *et al.* Effects of ritonavir and cobicistat on dolutegravir exposure: when the booster can make the difference. *J Antimicrob Chemother* 2017; **72**: 1842-4.
27. Song I, Min SS, Borland J *et al.* The effect of lopinavir/ritonavir and darunavir/ritonavir on the HIV integrase inhibitor S/GSK1349572 in healthy participants. *J Clin Pharmacol* 2011; **51**: 237-42.
28. Else L, Watson V, Tjia J *et al.* Validation of a rapid and sensitive high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) assay for the simultaneous determination of existing and new antiretroviral compounds. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010; **878**: 1455-65.
29. Penchala SD, Fawcett S, Else L *et al.* The development and application of a novel LC-MS/MS method for the measurement of Dolutegravir, Elvitegravir and Cobicistat in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci* 2016; **1027**: 174-80.
30. Cottrell ML, Hadzic T, Kashuba AD. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. *Clin Pharmacokinet* 2013; **52**: 981-94.

31. PREZISTA™ (Tibotec, Inc.) (Darunavir). Full prescribing information. Food and drug administration. 2008. [cited 2018 Apr 31]. Available from: http://accessdata.fda.gov/drugsatfda_docs/label/2008/021976s003s004lbl.pdf.
32. Reese MJ, Savina PM, Generaux GT *et al.* In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. *Drug Metab Dispos* 2013; **41**: 353-61.
33. Lepist EI, Phan TK, Roy A *et al.* Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, in vitro. *Antimicrob Agents Chemother* 2012; **56**: 5409-13.
34. Milburn J, Jones R, Levy JB. Renal effects of novel antiretroviral drugs. *Nephrol Dial Transplant* 2017; **32**: 434-9.
35. Dickinson L, Khoo S, Back D. Differences in the pharmacokinetics of protease inhibitors between healthy volunteers and HIV-infected persons. *Curr Opin HIV AIDS* 2008; **3**: 296-305.

TABLES AND FIGURES

Table 1: Dolutegravir (DTG), darunavir (DRV) and cobicistat (COBI) steady state pharmacokinetic (PK) parameters, expressed as geometric mean (GM), 90% confidence intervals (CI), coefficient of variation (CV) and GM Ratios (GMR, alone/co-administered).

Cmax: maximum concentrations, AUC: area under the curve, C_{24h}: concentration measured 24 hours post-dose.

Figure 1: Diagram illustrating study design.

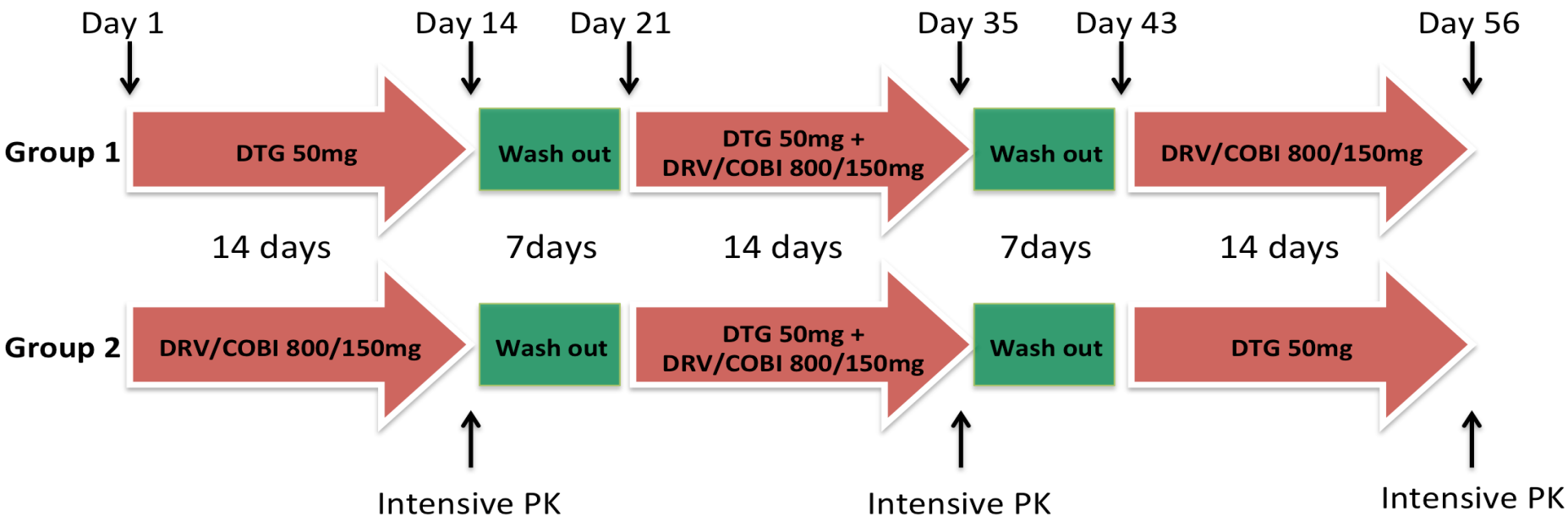
Figure 2: GM dolutegravir concentrations over 24 hours with and without DRV/COBI.

GM: geometric mean, DTG: dolutegravir, DRV: darunavir, COBI: cobicistat. $IC_{90:}$ (protein adjusted) inhibitory concentration.

Figure 3: GM darunavir concentrations over 24 hours with and without dolutegravir

GM: Geometric Mean, DTG: dolutegravir, DRV: darunavir, COBI: cobicistat, EC_{90}: (protein-adjusted) effective concentration

Figure 1: Diagram illustrating study design



	GM C_{max} (90%CI) (ng/mL)					GM $AUC_{0\text{-}24h}$(90% CI) (ng*h/mL)					GM C_{24} (90% CI) (ng/mL)				
	Alone	CV%	Combined	CV%	GMR	Alone	CV%	Combined	CV%	GMR	Alone	CV%	Combined	CV%	GMR
DTG	3398 (3087-3708)	23	3429 (3104-3755)	46	1.01 (0.92-1.11)	47669 (42377-52960)	28	45188 (40203-50174)	28	0.95 (0.87-1.04)	952 (795-1109)	40	852 (690-10145)	46	0.9 (0.80-1.00)
DRV	5364 (4726-6003)	31	4821 (4455-5187)	20	0.90 (0.83-0.98)	63222 (55152-71291)	33	58864 (52978-64750)	26	0.93 (0.86-1.00)	1146 (891-1400)	52	1070 (817-1322)	53	0.93 (0.78-1.11)
COBI	967 (868-1066)	27	929 (845-1014)	24	0.96 (0.89-1.04)	7829 (6865-8793)	32	7650 (6619-8682)	35	0.98 (0.88-1.08)	19 (10.4-28)	90	19 (6.7-31)	111	0.98 (0.79-1.22)

Table 1: Dolutegravir (DTG), darunavir (DRV) and cobicistat (COBI) steady state pharmacokinetic (PK) parameters, expressed as geometric mean (GM), 90% confidence intervals (CI), coefficient of variation (CV) and GM Ratios (GMR, alone/co-administered). C_{max}: maximum concentrations, $AUC_{0\text{-}24h}$: area under the curve, C_{24h}: concentration measured 24 hours post-dose.

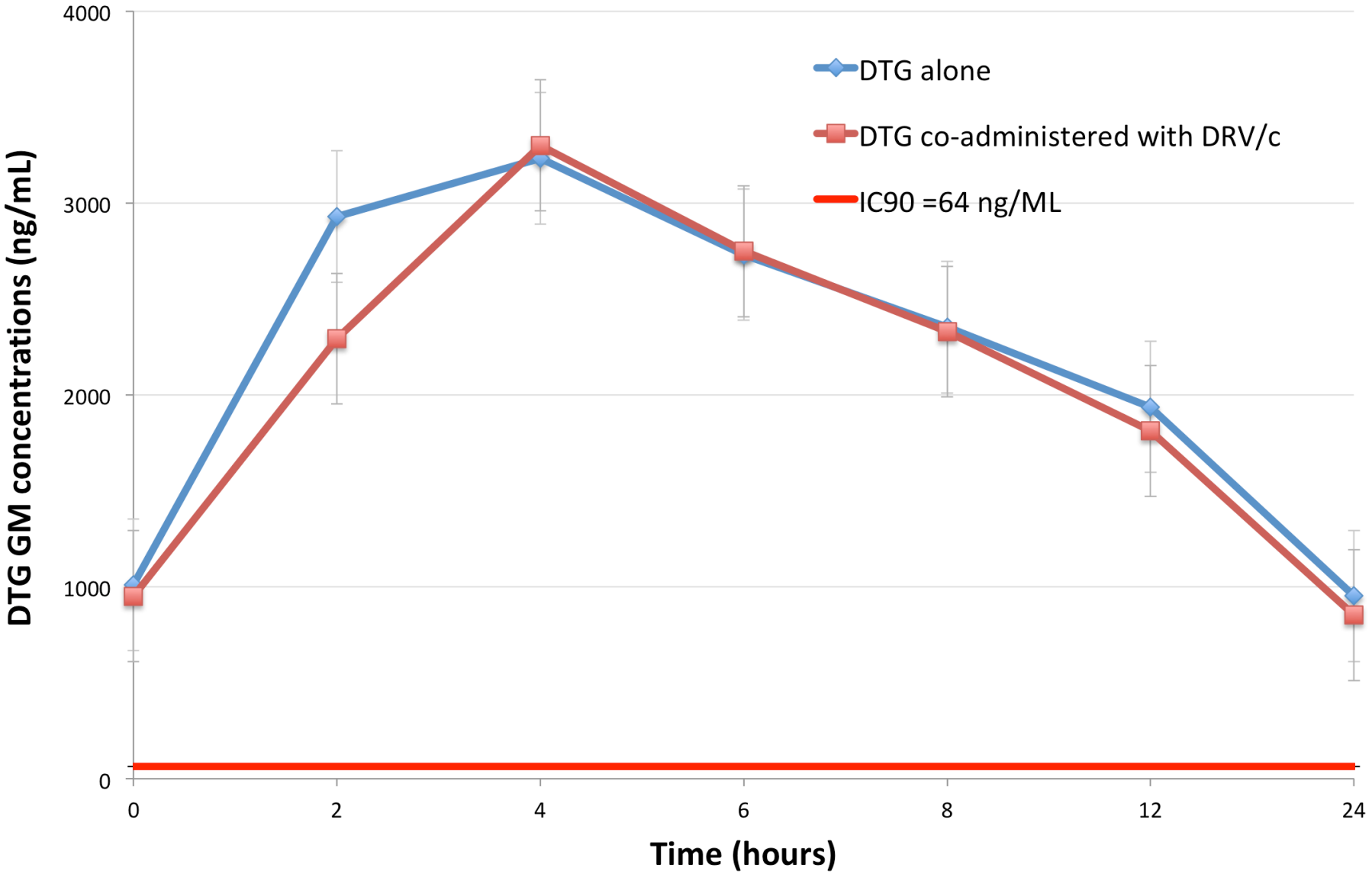


Figure 2: GM dolutegravir concentrations over 24 hours with and without DRV/COBI.
GM: geometric mean, DTG: dolutegravir, DRV: darunavir, COBI: cobicistat. IC_{90}: (protein adjusted) inhibitory concentration.

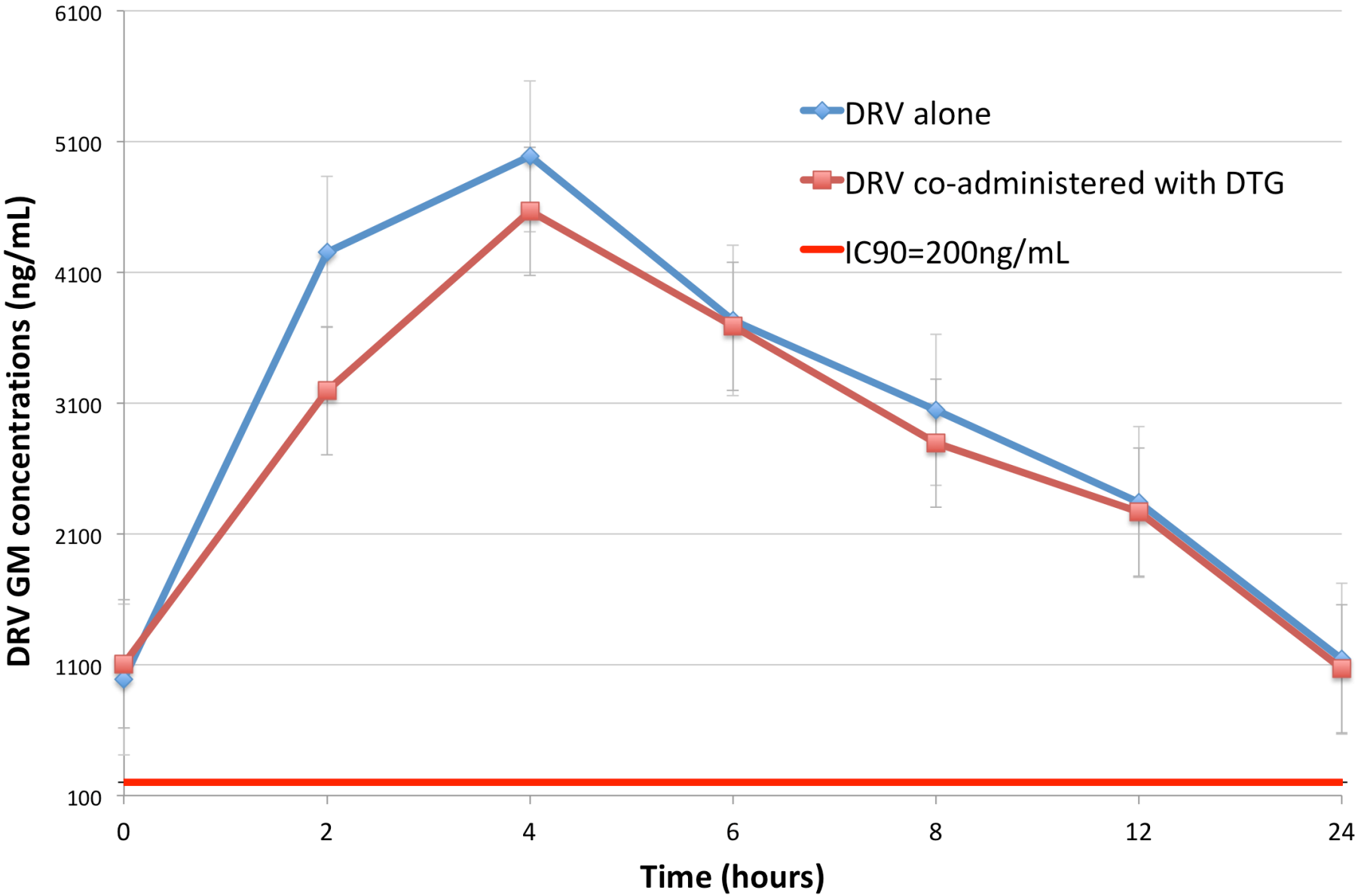


Figure 3: GM darunavir concentrations over 24 hours with and without dolutegravir
GM: Geometric Mean, DTG: dolutegravir, DRV: darunavir, COBI: cobicistat, IC_{90}: (protein-adjusted) inhibitory concentration