Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition

Emilie R. Elliot[1], Xinzhu Wang[2], Suveer Singh[2,4], Bryony Simmons[2], Jaime H Vera[3], Robert F Miller[5], Colin Fitzpatrick[3], Graeme Moyle[4], Myra McClure[2], Marta Boffito[1,2]

[1]St. Stephen's AIDS Trust–Chelsea and Westminster Hospital, London, UK, [2]Imperial College, London, UK, [3]Brighton and Sussex Med School, Brighton, UK, [4]Chelsea and Westminster Hospital, London, UK, [5]Mortimer Market Centre, Institute for Global Health, University College London, UK,

Corresponding author:

Dr Emilie Elliot

St. Stephen's Centre – Chelsea and Westminster Hospital

369 Fulham road, London SW10 9NH

tel: +44(0)20 33156506

fax: +44(0)20 33155628

email: emilieelliot@doctors.co.uk

SUMMARY:

We report a 25% increase in Dolutegravir C_{max} in people living with HIV≥60yrs compared to younger subjects. Discontinuation rate was 4.6%; interestingly, PK parameters were not associated with sleep or cognition changes over six months in those who continued DTG.

This data was presented in part at the annual Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 February 2017, Seattle, USA and at the 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, 14-16th June 2017, Chicago, IL, USA

ABSTRACT

Background

Demographic data show an increasingly aging HIV population worldwide. Recent concerns over dolutegravir-related neuropsychiatric toxicity have emerged, particularly amongst older HIV patients. We describe the pharmacokinetics (PK) of dolutegravir (DTG) 50mg once daily in people living with HIV (PLWH) aged 60 and older. Additionally, to address the call for prospective neuropsychiatric toxicodynamic data, we evaluate changes in sleep quality and cognitive function after switching to abacavir (ABC)/lamivudine (3TC)/DTG, over 6 months in this population.

Methods

PLWH aged≥60years with HIV-RNA<50copies/mL on any non-DTG based antiretroviral combination were switched to ABC/3TC/DTG. On day 28, 24-hour PK sampling was undertaken. Steady-state PK parameters were compared to a published historical control population aged≤50years. Six validated sleep questionnaires and neurocognitive (Cogstate®) testing were administered pre-switch and over 180 days (NCT02509195).

Results: Forty-three participants were enrolled; 40 completed the PK phase. Overall, five discontinued (two due adverse events, both sleep related, 4.6%). DTG maximum concentration (C_{max}) was significantly higher in patients≥60 versus controls (GM 4246ng/mL versus 3402ng/mL, p=0.005). In those who completed day 180 (n=38), sleep impairment was higher at day 28 (PSQI median global score 5.0 versus 6.0 p=0.02) but not at day 90 or 180. Insomnia, daytime function, fatigue test scores did not change statistically over time.

Conclusion:

DTG C_{max} was significantly higher in older PLWH. Our data provides clinicians with key information on the safety of prescribing DTG in older PLWH.

<u>KEY WORDS</u>: Aging, HIV, Dolutegravir, Pharmacokinetics, Sleep

INTRODUCTION

By 2015, one in three people accessing HIV care in the UK [1] and almost half in the US were aged 50 and over [2]. With advancing age, several physiological changes affect drug pharmacokinetics (PK) and pharmacodynamics (PD) [3].

The integrase inhibitor (InSTI) dolutegravir (DTG) is now the drug of choice for many HIV providers, thanks to high efficacy firmly demonstrated in trials and retained activity against some InSTI-resistant HIV-1 phenotypes [4]. Its low potential for drug-interactions is also an advantage in managing older people living with HIV (PLWH) [5]. DTG is a recommended key drug in major HIV guidelines and is a strong candidate to become first option in the WHO antiretroviral guidelines [6, 7].

In pre-marketing trials, DTG demonstrated favorable safety and tolerability profiles, with a <2% discontinuation rate secondary to any adverse events (AEs), comparable to raltegravir and superior to efavirenz [8, 9]. However, contrasting real-life data reveal unexpectedly higher rates (7-15%, median time 72 days) [10-14], most commonly due to insomnia/sleep disturbances and other neuropsychiatric (NP) AEs (up to 8%), regardless of prior neuropsychiatric history, thereby implicating a potentially neurotoxic effect of DTG [14-18]. Comparison studies suggest that NP-AEs are commoner with DTG than other InSTIs [11, 12, 16]. Interestingly, in several reports, DTG discontinuation was significantly higher in PLWH>60 years old [13, 16, 19], a group under-represented in licensing trials. This prompted a call in the literature for prospective studies evaluating DTG-associated AEs, including PK, sleep architecture analysis and neuropsychological testing, particularly in special populations [20].

A high prevalence of sleep disturbances is already described in the HIV population, even in the cART era, (30-73% *versus* 10-20% in the general population [21, 22]) and it is strongly associated with poorer disease outcomes, cognitive impairment and HIV-associated dementia [21, 23].

It is, therefore, important to characterise the role of aging on DTG PK/PD, especially with regards to central nervous system (CNS) toxicity and sleep disturbances. The primary objectives of this study were to describe the steady state PK of DTG 50 mg once daily (OD) in PLWH≥60 years and compare them to a published younger population (from the SINGLE trial [9]). The secondary objectives were to evaluate, in detail, changes in sleep and cognition over six months following a switch from non-DTG-based cART to abacavir (ABC), lamivudine (3TC) and DTG, as a fixed dose combination (FDC) tablet.

We hypothesised that age-related changes in drug PK might impact DTG, except its metabolism since it is mainly by UDP-glucuronosyltransferase-1A1 (UGT1A1) and no evidence supports age-related glucuronidation changes [24]. We also expected a reverse-association between sleep/cognition changes and PK parameters, particularly at the high end of the therapeutic range (or higher).

METHODS

Participants

Written informed consent was obtained from male and female PLWH, stable on cART, aged≥60 years with a body mass index (BMI) 18-35 kg/m^2. The protocol required that approximately 70% of subjects be ≥65 years (to ensure a variable age range). Eligibility criteria included plasma HIV-RNA<50 copies/mL at screening and no history of treatment failure or documented significant drug resistance on viral genotyping. With ABC use, a negative HLA-B*5701 allele result was required and participants were screened for cardiovascular (CV) risk using the QRISK2 calculator [6, 25] (eligible if 10-year risk of CV event was <20% or if risk factors were well controlled with medication/lifestyle measures). Participants were excluded if they had: significant acute/chronic illnesses; abnormal physical examination, ECG or laboratory determinations or use of known interacting drugs/remedies. No patients had preceding Primary Sleep Disorder diagnoses. The study was approved by the London Central Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA) and ran in accordance with Good Clinical Practice and the Declaration of Helsinki (NCT02509195).

Study design

This was a four-centre, 180-day (excluding screening and follow-up), open-label, prospective PK/PD study. After screening, eligible subjects were switched to ABC/3TC/DTG 600/300/50 mg FDC (Triumeq®) on day 1, one pill OD, orally, in the morning with or without breakfast for the study period, except on day 28. On D28, subjects underwent intensive DTG PK determinations, having fasted for six hours pre-dose and four hours post-dose to match the SINGLE PK sub-study circumstances [9]. Blood samples were collected pre-dose, 1, 2, 3, 4, 8, 12 and 24 hours post-dose. Study medications safety was evaluated using the National Institute of Allergy and Infectious Diseases Division of AIDS (NIAID2004). Medication compliance was assessed through direct questioning and pill count.

Collection and quantification of plasma dolutegravir

Whole blood samples were collected at each time-point on D28, from an indwelling venous catheter, into 6 mL spray-coated EDTA tubes, Following centrifugation, plasma was aliquoted equally into three 2.0mL tubes (Sarstedt, Germany) and stored at -80^{o}C. Samples were then shipped on dry ice to the Jefferiss Trust Laboratory (Imperial College London). DTG plasma concentrations were determined using ultra-performance liquid chromatography (UPLC) coupled with UV detection [26].

The assay calibration range was 0.25-10 mcg/ml, intra-assay variability 3.3%-6.1% and inter-assay variability 4.5%-5.7%. Overall accuracy was between 90.7% and 97.7% for three different quality control sample concentrations. The laboratory adheres to the ARV International Inter-laboratory Quality Control Program [27].

Pharmacokinetic and statistical analysis

A sample size of 40 subjects was calculated to provide at least 80% power to detect DTG PK parameter changes in older people against 16 controls. The calculated parameters were plasma concentration measured 24 hours after the observed dose (C_{24}), maximum observed plasma concentration (C_{max}), area-under-the-plasma-concentration-curve from 0 to 24 hours ($AUC_{0–24}$) and half-life ($t_{1/2}$). All PK parameters were calculated using actual blood sampling time and non-compartmental modelling techniques (WinNonlin-Phoenix, version 7.0). Descriptive statistics, including geometric mean (GM), 95% confidence interval (CI) and percentage coefficient of variation (CV%=100*standard deviation/mean) were calculated for DTG PK parameters at all time-points on D28, and compared to those obtained from the SINGLE PK sub-study control HIV population (≤50 years, n =16) [9] using non-parametric Mann-Whitney U test.

Sleep and cognitive data collection

Six published and validated self-reported paper questionnaires (table1) [28-33], recording different aspects of sleep, were administered to participants at baseline and on days 28, 90 and 180 in order to provide a comprehensive description of sleep quantity, quality and impact on daytime function, wakefulness, mental status and general wellbeing before and after medication switch. Answers to each question were coded as per questionnaire protocols (supplementary material) and entered into Excel for scoring.

Neurocognitive testing was carried out on D1 and D180 using the validated, widely used Cogstate® computerised assessment software [34], which evaluates a range of cognitive functions through eight domains: detection (DET)/identification (IDN) (speed of performance); card learning (OCL), one back memory (OBM)/two back memory (TWOB) (accuracy of performance); Groton Maze learning (GML), Groton Maze recall (GMR), and set-shifting (SETS) (number of errors made on testing). Participants completed a mock practice at screening to minimise learning effect.

Sleep and cognitive data analysis

Sleep baseline characteristics and outcome measures at each time-point were descriptively summarised using medians, interquartile ranges (IQR), and proportions. Composite scores for sleep questionnaires were calculated and interpreted as per questionnaire protocols and cut-offs (table 1). Neurocognitive scores were analysed using Cogstate® recommendations [35]. Changes in cognitive scores were calculated for each subject for each domain (baseline-D180), and were standardised according to the within-subject standard deviation (WSD). The score sign was reversed where appropriate so positive values represent improvement for all domains. A composite score for the change from baseline was calculated by averaging the standardised change scores across all Cogstate® tasks for each individual.

As data was not normally distributed, non-parametric tests were used for analysis. Changes in sleep and cognitive scores from baseline to each time-point were tested for significance using the Wilcoxon sign-rank test. Spearman's correlation examined correlations between outcomes and DTG PK parameters.

As efavirenz use is associated with NP-AEs, especially sleep disturbances [6], a sub-analysis was conducted using the Mann-Whitney test to compare individuals who switched from an efavirenz-based regimen to those who didn't, thereby preventing efavirenz removal from potentially masking DTG effects.

Internal consistency was evaluated for outcomes with multiple domains using Cronbach's α and corrected component-total Spearman's rho (r_s) correlations α ($\geq$.70 and $r_s \geq$.30 indicated adequate internal consistency). Correlation between different sleep questionnaires was evaluated at baseline to determine the level of agreement.

Statistical analyses were performed using Stata (version 14.1) and GraphPad Prism (version 7.03). In the analyses, p-values, uncorrected and corrected for multiple comparisons, were calculated; $p<0.05$ was deemed significant.

RESULTS

Study population

Fifty-three subjects were screened; 43 enrolled and received at least one study drug dose. Three/43 participants withdrew before D28 and could not be included in the PK analysis (two moved abroad and one experienced fatigue and photosensitivity attributed to the study drugs). Forty participants completed the PK phase and 38 attended the final study visit (D180). One participant withdrew secondary to insomnia/vivid dreams (resolved by switching to tenofovir/emtricitabine/raltegravir) and the other withdrew for job relocation; both were included in D28 PK and PD analyses. Subject and control characteristics are summarised in table 2.

Dolutegravir plasma pharmacokinetics

Figure 1 demonstrates GM DTG concentration-time curves for the observed and control populations. Steady-state PK parameters are summarised in table 3.

There were no differences in DTG AUC_{0-24}, C_{24} or $t_{1/2}$ between the two populations. However, C_{max} (approximately two hours post-dose in both groups) was significantly higher in subjects≥60 years old (GM 4246 *versus* 3402 ng/mL, p=0.005).

Sleep questionnaire results at baseline and follow up

Detailed response rates and median (IQR) scores per questionnaire, domain and time-point are in the supplementary file, table A and figure B.

- *Overall sleep impairment: Pittsburgh Sleep Quality Index (PSQI) [28]*

Median global PSQI score was higher at D28 versus baseline (5.0 *versus* 6.0, p=0.02 adjusted for multiple testing) but at no other time-points. No domain achieved statistical significance individually.

Internal consistency was acceptable for the global score (α=0.72). Corrected component-total correlations ranged from 0.19 (daytime dysfunction) to 0.66 (quality).

- *Insomnia: Insomnia Severity Index (ISI) [29]*

Median (IQR) global ISI scores remained stable (range 5-6.5); four individuals developed moderate insomnia over time (ISI 14-21; not significant) and one subject's severe insomnia (ISI>21) improved whilst another's developed by D28 leading to discontinuation (described above).

- *Daytime sleepiness: Epworth Sleepiness Scale (ESS) [30]*

At baseline, 29% individuals were considered 'sleepy' (ESS>10) compared with 24% at D180 (not significant).

- *Daytime function: Functional Outcomes of Sleep Questionnaire (FOSQ) [31]*

Median (IQR) global FOSQ remained stable from baseline to day D180 (range 18.01-18.81/20) with a generally good level of daytime function across the cohort.

- *Fatigue severity: Fatigue Severity Scale (FSS) [32]*

At baseline, four/39 (10%) individuals reported having fatigue; this was 20% on D180 (not significant).

- *Risks for possessing a sleep disorder: Sleep Disorder Questionnaire (SDQ) [33]*

No participants met the diagnostic criteria at baseline for any of the four sleep disorders tested and no significant change in scores was observed over time.

- *Correlation between sleep measures*

There was a significant correlation between all sleep measures evaluated by more than one questionnaire across all scores at baseline (.37<*r*<.83; p<.05).

- *Sleep scores by efavirenz status*

Seventeen/40 (43%) subjects switched from an efavirenz-based combination. At baseline, some measurements appeared worse in individuals who did not switch from efavirenz. No significant difference was observed between groups in overall score changes at each time-point compared to baseline for all questionnaires except ISI, which improved over 180 days in participants without efavirenz in their previous regimen and worsened in those with (p=0.02); however this did not remain after adjustment for multiple comparisons (p>0.05) (supplementary file, table C).

- *Relationship between sleep scores and PK parameters*

There was no correlation between DTG PK parameters and D180 sleep scores or intra-subject change in global scores over 180 days (delta test scores) (figure 2; supplementary file, tables D and E). To rule out an effect dependent on a drug level threshold, the Mann-Whitney test was used to compare delta test scores in subjects with C_{max} above the upper quartile (Q4) to those below (Q1-3). There were no differences (0.62<p-value<1.0); nor with 95th centile C_{max} used as threshold (0.13<p-value<0.73). Similarly, there was no difference in C_{max} between D180 test score or delta test score low and high quartile groups for all sleep questionnaires ((0.31≤p-value≤0.66 and 0.63<p-value<1.0).

Changes in cognitive scores (table 4)

Between baseline and D180, no change in global cognitive composite scores and individual domain scores was observed over time except GML (executive function) where a significant improvement from baseline to D180 was seen (median change (IQR) 0.32 (0-0.74), unadjusted p=0.002).

There was no correlation between C_{24} and AUC_{0-24} and D180 cognitive function or delta cognitive scores (individual domains and global composite scores; p=0.07). Unexpectedly, higher C_{max} was associated with *improvements* in global cognitive function (r=0.39, p=0.02; figure 2). The improvement in median (IQR) delta score was higher in those with a C_{max}>upper 95%CI than in those below (p=0.0195).

Clinical safety and efficacy

Two/43 (4.6%) participants discontinued the study secondary to AEs (described above). In the remaining subjects, there were no virological failures or grade 3 or 4 toxicity following treatment initiation. The studied FDC was well tolerated.

DISCUSSION

We characterized the steady-state PK of DTG 50 mg OD in an aging HIV population, mostly over 65 years, the age associated with potential changes in drug PK [24]. Compared to the younger control group, C_{max} was significantly higher (25%) in those ≥60, indicating increased DTG absorption. Whilst the net effect of age-related physiological intestinal changes (e.g. reduction in pH, gastrointestinal motility etc.) on the absorption of most drugs is thought to be minimal [3], our findings could be explained by age-related alterations in expression of active DTG efflux transporters, such P-gP (P-glycoprotein) and BCRP (breast cancer resistance protein), across epithelial cells in the gastrointestinal tract [3, 24, 36]; however further research is required. There were no differences in DTG C_{24}, $AUC_{0\text{-}24}$ or $t_{1/2}$ between the two groups, supporting a lack of age-associated effect on the main DTG metabolic pathway (UGT1A1).

To address the call for prospective PD data [20, 37], we also describe the first post-marketing analysis of sleep and cognition-related PD changes, over 180 days following a switch to ABC/3TC/DTG. DTG-related NP-AEs (including insomnia) are an emerging concern [14-18] and older age has been described as an independent risk factor [13, 16, 19]. In our study, two participants discontinued DTG because of NP-AEs (4.6%), which is consistent with published cohorts (1.7-8%). However, when investigating sleep quality and Cogstate status in those who continued the drug, we only observed a small increase in PSQI scores at D28, which resolved by D90, and a non-significant trend towards an increase in FSS score. Other scores remained stable or improved following the introduction of DTG. Whilst the one subject who withdrew secondary to NP-AEs had elevated levels of DTG, we did not find any association between DTG PK parameters and changes in sleep scores in the remaining subjects over time, which is in keeping with observations from Riva [38] and Hoffman [39]. There were also no changes in sleep scores in subjects with very high drug concentrations in whom, surprisingly, cognition improved significantly. These interesting findings suggest that the mechanisms of DTG-related neurotoxicity are likely to be more complex than a simple linear or threshold-defined PK relationship and may relate to a combination of factors, including pharmacogenetic, immune and/or functional predispositions.

Of interest, Yagura et al found that DTG C_{24h} ($\geq$1.06 μg/mL) correlated with CNS side effects in younger Japanese PLWH. No significant difference in DTG concentration was, however, observed with individual symptoms or insomnia. The researchers subsequently reported a weak association with UGT1A1*6 and UGT1A1*28 alleles [40].

Capetti *et al*. found DTG-related sleep disorders resolved in some patients switching to morning dosing (0.9% *versus* 3.5%) [19]. In our study, subjects were dosed in the morning to allow for steady state PK measurements; this could partially explain the absence of new sleep disturbances, although others researchers report unchanged rates with morning dosing [20, 40]. Our subject population was a group of only mildly sleep-disturbed individuals from baseline, which may also partially explain the lack of positive findings in those who completed the study. Overall, whilst sleep impairment rates (PSQI>5) at baseline, matched that historically reported in the HIV literature (44-51%), scores were only just in the lower range of abnormal ($\leq$7). Additionally, the prevalence of subjects with moderate insomnia (ISI) in our cohort (7-21%) is below that previously reported in PLWH [21].

Controlling for a switch from efavirenz did not change the lack of positive results, likely due to the fact that efavirenz subjects in our study were those who do not experience sleep disturbances on it.

There are limitations to our study. Our subjects were predominantly male, thereby not fully representative of real life cohorts. DTG NP-AEs are thought to be higher in women, but this is an *independent* risk factor. Importantly, our study was not powered to detect changes in sleep quality but for the ability to detect PK differences between younger and older PLWH, PD results should therefore be interpreted with caution (although our numbers mirrored previous HIV sleep studies [21] and consistency across sleep tools (measuring the same effect) suggest that results are accurate). Furthermore, the use of self-reported questionnaires may compromise intra- and inter-subject consistency and lead to recall bias. The effect of suggestion may also introduce bias as was proposed by the authors of the SINGLE trial (efavirenz *versus* DTG) [9] to explain higher rates of DTG-related sleep disturbances. Although validated in the general population, our sleep questionnaires are not validated in aging PLWH. However, a good correlation between direction changes, reflects good inter-questionnaire reliability. Finally, the use of historical controls is a limitation, which should be addressed in future studies with a larger and active control arm.

The strengths of our study lie in its prospective and controlled design, investigating a special population growing in size and in need of data to tailor HIV treatment appropriately. Additionally, we are the first group to characterise detailed sleep and cognitive data in PLWH following Triumeq® introduction and to explore the DTG PK/PD relationship in aging PLWH. The use of multiple questionnaires allowed a more comprehensive evaluation of sleep and its effects than previously reported.

In conclusion, we showed a significantly higher DTG C_{max} in PLWH≥60 *versus* younger subjects. The discontinuation rate was similar to previous real-life reports but the C_{max} increase was not associated with sleep or cognitive decline over six months. This data informs physicians and patients on the safety and tolerability of DTG in older patients, particularly following the early period where careful monitoring remains recommended [11].

NOTES:

Author contributions

EE and BS wrote the manuscript; MB and SS designed the research; EE, MB, XW, JHV, CF and RB performed the research; BS, XW and EE analysed the data, XW and MM provided analytical tools and all authors reviewed and contributed to the final manuscript.

Acknowledgements

We acknowledge the following for permission to use the sleep questionnaires: LB Krupp, State University of New York, USA; MW Johns, Epworth Hospital, Melbourne, Australia; DJ Buysse, University of Pittsburgh School of Medicine, USA; CH Bastien, Université Laval, Ste-Foy, Quebec, Canada; TE Weaver, School of Nursing, Philadelphia, USA. The authors acknowledge the contribution of and thank Mrs Ana de Castro-Brito, who helped compile and distribute the multiple sleep questionnaires. We acknowledge Dr Nicole Pagani and Susanna Wong for their substantial contributions. The authors would like to thank the research team at St Stephen's Clinical Research for their hard work and the volunteers who took part in the study. The study also acknowledges the contribution of the NIHR BRC at Imperial College London.

Funding:

This work was supported by a research grant from ViiV Healthcare. Funding support was also provided by the St. Stephen's AIDS Trust.

Conflict of interest/Disclosures:

ERE reports grants from ViiV Healthcare Ltd, during the conduct of the study; other from Gilead sciences Ltd, outside the submitted work.SS reports personal fees from Ambu, outside the submitted work. **BS** reports personal fees from St. Stephen's AIDS Trust, during the conduct of the study; personal fees from St. Stephen's AIDS Trust, outside the submitted work. **JHV** has received honoraria and research grants, been a consultant or investigator in trials sponsored by Merck, Janssen Cilag, Piramal and Gilead sciences. He has received sponsorship to attend scientific conferences from Janssen Cilag, Gilead Sciences and AbbVie. He is also a trustee for the Martin Fisher Foundation. **RM** has received lecture fees from Gilead, Merck and Janssen for giving non-promotional talks on clinical aspects of HIV infection, and grant from Gilead for attending a conference. **GM** reports grants from ViiV Healthcare Ltd, during the conduct of the study; personal fees from Gilead Sciences Ltd, personal fees from Merck, personal fees from Thera Technologies, personal fees from Trio Health:, outside the submitted work. **MB** had received travel and research grants from and has been advisor/speaker for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva. All other authors had no conflicts of interest to disclose.

REFERENCES

1. Public Health England. Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK - 2017 report. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/675809Towards_elimination_ofHIV_transmission_AIDS_and_HIV_related_deaths_in_the_UK.pdf.

2. HIV Among People Aged 50 and Over. Centres for Disease Control and Prevention (CDC).

3. Klotz U. Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev **2009**; 41(2): 67-76.

4. 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(3): 354-62.

5. Marzolini C, Back D, Weber R, et al. Ageing with HIV: medication use and risk for potential drug-drug interactions. J Antimicrob Chemother **2011**; 66(9): 2107-11.

6. Waters L. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf. BHIVA. Accessed 19 December 2017.

7. Cahn P. Candidates for inclusion in a universal antiretroviral regimen: dolutegravir. Curr Opin HIV AIDS **2017**; 12(4): 318-23.

8. Raffi F, Rachlis A, Stellbrink HJ, 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 **2013**; 381(9868): 735-43.

9. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med **2013**; 369(19): 1807-18.

10. Todd S, Rafferty P, Walker E, et al. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. Int J STD AIDS **2017**: 956462416688127.

11. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. AIDS **2017**; 31(13): 1853-8.

12. Penafiel J, de Lazzari E, Padilla M, et al. Tolerability of integrase inhibitors in a real-life setting. J Antimicrob Chemother **2017**; 72(6): 1752-9.

13. Bonfanti P, Madeddu G, Gulminetti R, et al. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. AIDS **2017**; 31(3): 455-7.

14. de Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS **2016**; 30(18): 2831-4.

15. Scheper H, van Holten N, Hovens J, de Boer M. Severe depression as a neuropsychiatric side effect induced by dolutegravir. HIV Med **2017**.

16. Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med **2017**; 18(1): 56-63.

17. Cailhol J, Rouyer C, Alloui C, Jeantils V. Dolutegravir and neuropsychiatric adverse events: a continuing debate. AIDS **2017**; 31(14): 2023-4.

18. Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS **2017**; 31(8): 1201-3.

19. Capetti AF, Di Giambenedetto S, Latini A, et al. Morning dosing for dolutegravir-related insomnia and sleep disorders. HIV Med **2017**.

20. Hoffmann C, Welz T, Sabranski M, et al. Reply to Letter 'Morning dosing for dolutegravir-related insomnia and sleep disorders' by Capetti et al. HIV Med **2017**.

21. Gamaldo CE, Gamaldo A, Creighton J, et al. Evaluating sleep and cognition in HIV. J Acquir Immune Defic Syndr **2013**; 63(5): 609-16.

22. Ram S, Seirawan H, Kumar SK, Clark GT. Prevalence and impact of sleep disorders and sleep habits in the United States. Sleep Breath **2010**; 14(1): 63-70.

23. Low Y, Goforth HW, Omonuwa T, Preud'homme X, Edinger J, Krystal A. Comparison of polysomnographic data in age-, sex- and Axis I psychiatric diagnosis matched HIV-seropositive and HIV-seronegative insomnia patients. Clin Neurophysiol **2012**; 123(12): 2402-5.

24. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. Br J Clin Pharmacol **2004**; 57(5): 540-4.

25. https://www.qrisk.org.

26. 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(3): 327-31.

27. 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(2): 239-43.

28. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res **1989**; 28(2): 193-213.

29. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med **2001**; 2(4): 297-307.

30. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep **1991**; 14(6): 540-5.

31. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep **1997**; 20(10): 835-43.

32. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol **1989**; 46(10): 1121-3.

33. Douglass AB, Bornstein R, Nino-Murcia G, et al. The Sleep Disorders Questionnaire. I: Creation and multivariate structure of SDQ. Sleep **1994**; 17(2): 160-7.

34. Cysique LA, Maruff P, Darby D, Brew BJ. The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery. Arch Clin Neuropsychol **2006**; 21(2): 185-94.

35. Winston A, Puls R, Kerr SJ, et al. Differences in the direction of change of cerebral function parameters are evident over three years in HIV-infected individuals electively commencing initial cART. PLoS One **2015**; 10(2): e0118608.

36. Mangoni AA. The impact of advancing age on P-glycoprotein expression and activity: current knowledge and future directions. Expert Opin Drug Metab Toxicol **2007**; 3(3): 315-20.

37. de Boer MG, Brinkman K. Recent observations on intolerance of dolutegravir: differential causes and consequences. AIDS **2017**; 31(6): 868-70.

38. Riva AP, A.; Rusconi, S. . Dolutegravir and unboosted atazanavir: a dual NRTI-and booster-free antiretroviral regimen simplification in HIV-1-infected patients with viral suppression. In: International Congress of Drug Therapy in HIV Infection 23 - 26 October 2016, Glasgow, UK P090.

39. Hoffmann C WE, Schewe K. CNS toxicity of DTG is not associated with psychiatric conditions or plasma exposure. CROI, March 4–7, 2018 | Boston, USA P424.

40. Yagura H, Watanabe D, Kushida H, et al. Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse

events in Japanese individuals infected with HIV-1. BMC Infect Dis **2017**; 17(1): 622.

Tables and Figures

Table 1: Summary of content, process and scoring of sleep questionnaires and cognitive testing

Table 2: Demographic and clinical characteristics of study participants and controls

Table 3: Dolutegravir steady-state PK parameters for the observed and control groups measured over 24 hours

Table 4: Change in neurocognitive scores (effect size)

Figure 1: DTG GM concentration-time curve in study population and controls over 24 hours

Figure 2: Scatter plots showing changes in sleep and neurocognitive scores over 180 days against Cmax

Table 1: summary of content, process and scoring of sleep questionnaires and cognitive testing

Questionnaire	Process	Main Domains	Recall period	Number of questions	Time to complete (minutes)	Scores
PSQI	Self- Reported 0-3 Likert scale	Sleep Quality, sleep Disturbance and sleep habits	1 month	19	5-10	Score of 5 or more indicates poor sleep quality Global score calculated by summing subscale scores (not calculated for individuals with missing results)
ESS	Self- Reported 0-3 Likert scale	Level of sleepiness/ propensity of falling asleep	N/A	8	< 5	≥11 indicates excessive daytime sleepiness
FOSQ	Self- Reported 0-4 Likert scale	Functional impairment in activities of daily living resulting from sleepiness	N/A	30	15	5 domains: for each domain, lower scores indicate more acute issues. Each domain score calculated by averaging answered domain questions. Global score calculated by averaging the subscale scores & multiplying by 5 (allows for missing subscale scores)
ISS	Self- Reported 0-4 Likert scale	Nature, severity and impact of insomnia	2 weeks	7	<5	0-7 no insomnia 8- 14 subthreshold insomnia 15-21 moderate insomnia 22-28 severe insomnia
FSS	Self- Reported 1-7 Likert scale	Effect of fatigue on motivation, exercise,	1 week	9	<5	>5 indicates abnormal fatigue

		physical, social and family functioning				
SDQ	Self- Reported 1-5 Likert scale	Sleep quality Sleep disturbance Daytime function Medication Medical family history	6 months	175	30	4 sleep disorders categories: Sleep Apnoea Syndrome, Narcolepsy, Periodic Limb Movements Disorders and Psychiatric sleep disorders.
Cogstate neurocognitive test	Computerised battery	Detection Identification Set Shifting Groton Maze Learning Groton Maze Recall One Card Learning One Back Memory Two Back Memory	N/A	8 tasks		Score provided for each of 8 domains using optimal outcome measure (as defined by Cogstate guidelines). Composite score for change from baseline calculated by averaging standardised change scores

Table 2: Demographic and clinical characteristics of study participants and controls

	Variable	Study subject in PK analysis (n=40)	Controls (n=16)
Age	Median (range) in years	66 (60-79)	36 (22-50)
Ethnicity (n)	White British/Irish/Other	33	11
	African Heritage	3	3
	Hispanic	2	0
	Asiatic	2	0
	American Indian/Alaskan Native	0	1
Gender (n)	Male	39	15
	Female	1	1
Pre-switch regimen			
Backbone (n)	Abacavir/Lamivudine (ABC/3TC)	16	N/A
	Tenofovir disoproxil fumarate/ Emtricitabine(TDF/FTC)	20	N/A
3rd Agent (n)	Boosted Protease Inhibitor (PI) (of which monotherapy and dual therapy with RAL)	9 (2 and 1)	N/A
	NNRTI (of which Efavirenz)	24 (17)	N/A
	Raltegravir (of which dual therapy with PI)	6	N/A
	Zidovudine (AZT)	1	N/A
Salvage Therapy (n)	FTC, Maraviroc, Darunavir, Ritonavir	1	N/A

NNRTI: Non Nucleotide Reverse Transcriptase Inhibitor; RAL: Raltegravir; N/A: Not Applicable

Table 3: Dolutegravir steady-state PK parameters for the observed and control groups, measured over 24 hours

Note: The PK parameters for the participant who withdrew secondary to NP-AEs after day 28 were: C_{max} 5300 ng/mL, C_{24} 2013 ng/mL, AUC 77942 hr*ng/mL and $t_{1/2}$ 19.8 hrs; all >95th percentile for the study group.

	Observed group (n=40)				**Control group (n=16)**				**P value (Mann-Whitney U)**			
	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{0-24} (ng.h/ml)	$t_{1/2}$ (hrs)	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{0-24} (ng.h/ml)	$t_{1/2}$ (hrs)	C_{max} (ng/ml)	C_{min} (ng/ml)	AUC_{0-24} (ng.h/ml)	$t_{1/2}$ (hrs)
Geomean	**4246**	1052	51799	12.84	**3402**	942	48068	14.35	**0.00496**	0.7718	0.5619	.7065
Low 95%	4018	999	49405	12.05	3008	799	42350	11.16	-	-	-	-
Up 95%	4767	1351	59020	14.93	4030	1461	59898	21.44	-	-	-	-
CV %	27	48	29	34	29	58	34	62	-	-	-	-

Table 4. Change in neurocognitive scores (Effect size)

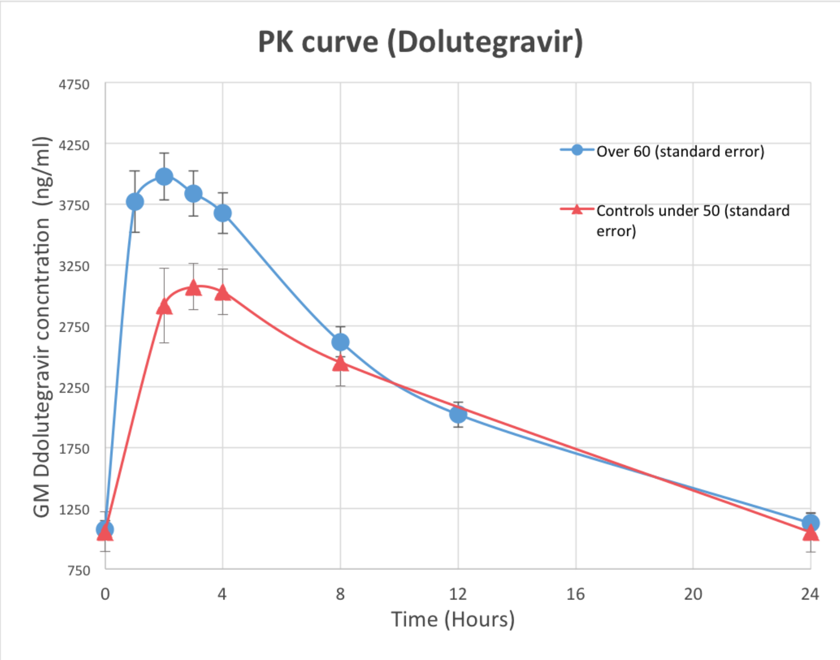
Cogstate domain	Cognitive function	Standardised change score (Day 180-baseline)		
		n	Median (IQR)	*p-value*
Detection task (DET)	Psychomotor function	37	0.02 (-0.16,0.13)	*0.743*
Identification task (IDN)	Attention	37	-0.04 (-0.47,0.58)	*0.602*
Set Shifting (SETS)	Executive function	37	0.05 (-0.32,0.75)	*0.471*
Groton Maze Learning (GML)	Executive function	34	0.32 (0.00,0.74)	*0.002***
Groton Maze Recall (GMR)	Delayed recall	35	0.27 (-0.82,1.37)	*0.176*
One Card Learning (OCL)	Learning	36	0.06 (-0.69,1.00)	*0.592*
One Back Memory (ONB)	Working memory - simple	37	0.24 (-0.90,0.77)	*0.908*
Two Back Memory (TWOB)	Working memory - complex	37	0.00 (-0.97,0.84)	*0.982*
Composite score		**37**	**0.16 (-0.23,0.37)**	***0.187***

	C_{max} <95th centile (n = 25)	C_{max} >95th centile (n=12)	*p-value*
Median Cogstate Delta score (IQR)	0.08 (0.30-0.20)	0.41 (0.12-0.64)	0.0195*

Note: for difference scores, score sign reversed for all outcome measures where increasing values indicate performance decline. Thus, for all measures, negative values indicate performance decline and positive values indicate performance improvement. Difference scores standardised according to within-subject standard deviation (WSD). Composite score for each subject calculated by averaging standardised change scores across all domains.

P-values are exact derived from Wilcoxon matched-pairs sign-rank test (not adjusted for multiple comparisons)

Figure 1.



PK curve (Dolutegravir)
GM Ddolutegravir concntration (ng/ml)
4750
4250
3750
3250
2750
2250
1750
1250
750
0
4
8
12
16
20
24
Time (Hours)
Over 60 (standard error)
Controls under 50 (standard error)

Figure 2.

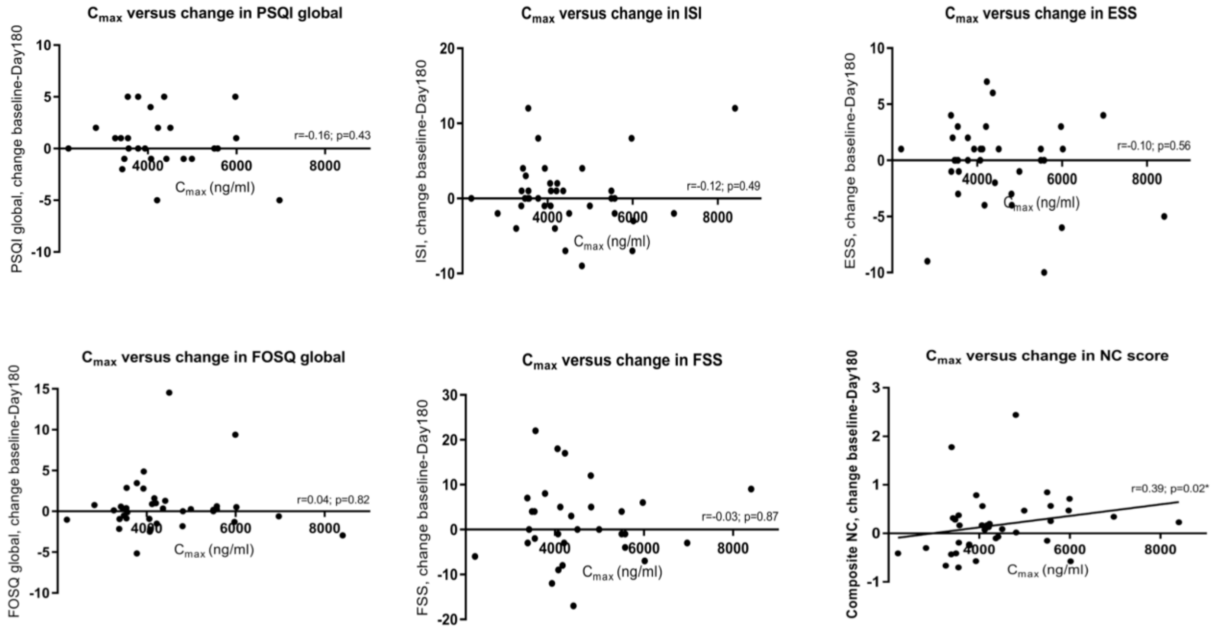


Figure 2: Scatter plots showing changes in sleep and neurocognitive scores over 180 days against Cmax