



# Relationship between dolutegravir plasma exposure, quality of sleep and its functional outcome in patients living with HIV over the age of 60 years

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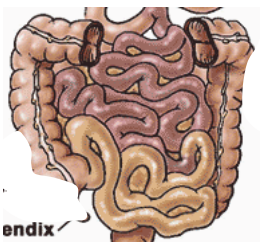
# Background I

- DTG potent second generation HIV INSTI increasingly being prescribed to PLWH
- DTG-related CNS AEs have been shown to:
  - 1. Occur less frequently than when prescribing EFV
  - 2. Occur in up to 5% of PLWH enrolled in prospective clinical trials with low discontinuation rates
  - 3. Lead to discontinuation in up to 5% of PLWH in observational cohorts
- Whether DTG systemic exposure correlates with the development of CNS AEs unclear

# Background II

- Older patients often underrepresented in trials
- Changes in drug PK with ageing

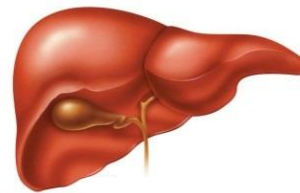
## Absorption



## Distribution



## Metabolism



## Renal elimination



# Objectives

## Primary objective:

-To assess the steady state **pharmacokinetics** of dolutegravir 50 mg once daily in HIV-infected subjects of 60 years or greater

## Secondary objectives:

-To assess the **safety, tolerability, patient quality of life and sleep quality** and maintenance of HIV viral load control of abacavir/lamivudine/dolutegravir once daily in HIV-infected subjects of 60 years or greater

-To measure the **metabolic profile** in patients over the age of 60 with HIV infection who switch antiretroviral regime (metabonomics)

-To investigate cerebral function via **cognitive testing** before and after a switch in antiretroviral therapy to dolutegravir containing regimens

-To investigate the relationship between **genetic polymorphisms** and exposure to dolutegravir

# Study design

## Day 1

- Examination
- Concomitant meds
  
- Safety bloods
- Urinalysis
- Viral load

**Switch to  
ABC/3TC/DTG**

Quality of life and  
Full Sleep Quality  
questionnaire set

Neurocognitive  
testing

## Day 14

- Adherence
- Concomitant meds
  
- Symptom-directed examination
- Adverse events review (AEs)
- Safety bloods
- Viral load

## Day 28

- Adherence check
- Concomitant meds
- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Witnessed dosing on an empty stomach
- **Intensive PK sampling**

Quality of life and  
Short Sleep Quality  
questionnaire set

## Day 90

- Adherence
- Concomitant meds
  
- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Viral Load
- DTG C<sub>min</sub>

Quality of life and  
Short Sleep Quality  
questionnaire set

## Day 180

- Adherence
- Concomitant meds
  
- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Viral Load
- DTG C<sub>min</sub>

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## Day 28

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- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Viral load

Intensive DTG PK  
sampling

Quality of life and  
Short Sleep Quality  
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Quality of life and  
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- Safety bloods
- Urinalysis
- Viral Load
- DTG C<sub>min</sub>

Quality of life and  
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# Materials & Methods

Protocol required enrolment of PLWH aged  $\geq 60$  years (30%) and  $\geq 65$  years (70%), with HIV-RNA  $< 50$  copies/mL on any cART, HLAB5701 negative

All switched to ABC/3TC/DTG (from different cART, 43% from efavirenz-containing regimens) on Day 1

On day 28, PK sampling over 24 h undertaken in a fasted state and PK parameters compared to those obtained from the PK sub-study of SPRING-1 (PLWH  $< 50$  years underwent full DTG PK in a fasted state, historical data)

Sleep questionnaires were administered at baseline (before switching to ABC/3TC/DTG) and 28 days following ABC/3TC/DTG initiation

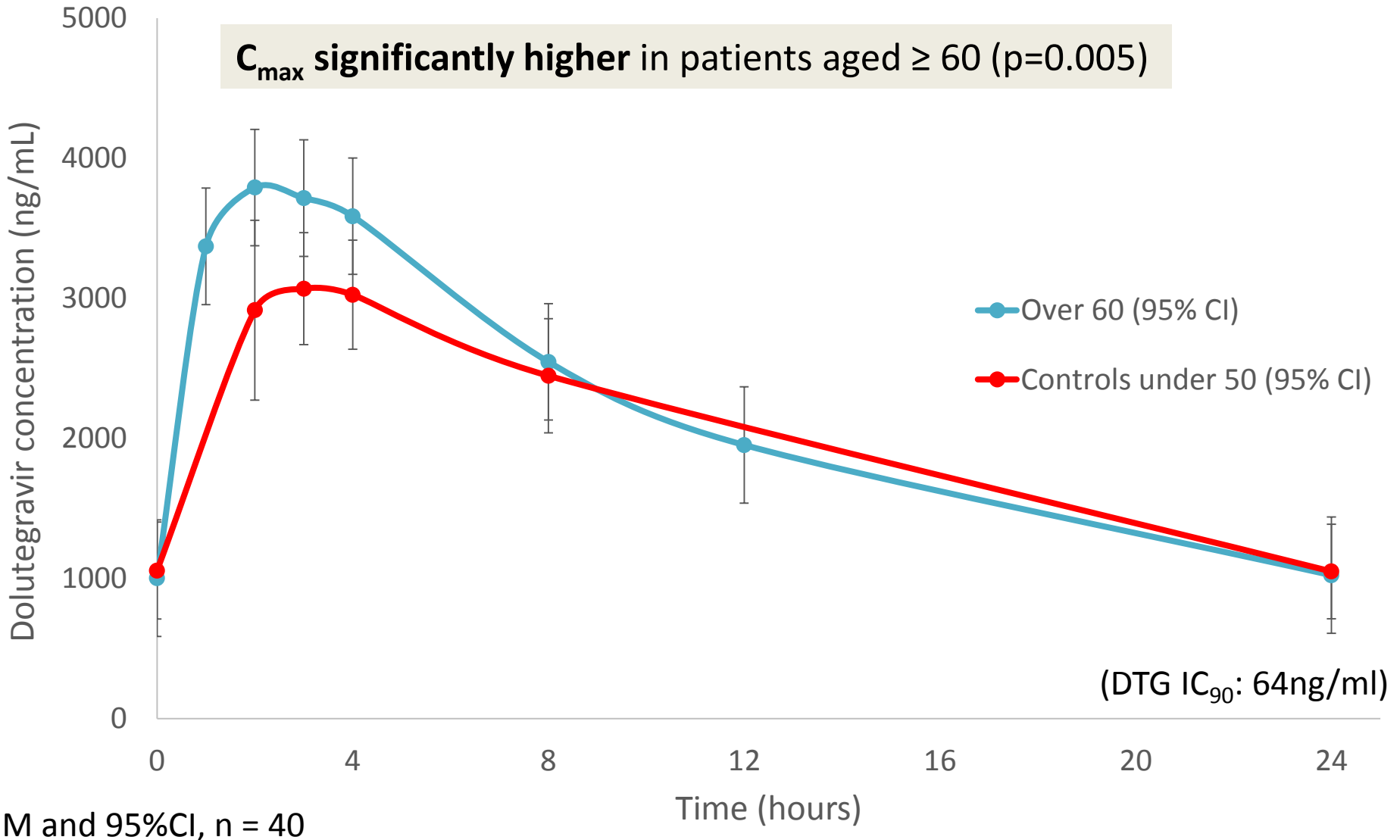
Non-parametric testing (Mann–Whitney U test, Spearman's rank correlation coefficient) was used to compare DTG PK in the two groups and to compare questionnaire outcomes at baseline versus day 28 to investigate whether there was a **correlation between DTG PK parameters and sleep questionnaire results**

# Sleep questionnaires

<u>Sleep Questionnaire</u>	Main Domains	Scores
<b>Pittsburgh Sleep Quality Index (PSQI)</b>	<b>Sleep quality</b> , sleep disturbance and sleep habits	Score of 5 or more indicates poor sleep quality
<b>Epworth Sleepiness Scale (ESS)</b>	Level of <b>sleepiness</b> / propensity of falling asleep	>=11 Excessive daytime sleepiness
<b>Functional Outcomes of Sleep (FOSQ)</b>	<b>Functional impairment</b> resulting from sleepiness in ADLs	5 domains: for each domain, lower scores indicate more acute issues
<b>Insomnia Severity Index (ISI)</b>	Nature, severity and impact of <b>insomnia</b>	0-7 no insomnia 8- 14 subthreshold insomnia 15-21 moderate insomnia 22-28 severe insomnia
<b>Fatigue Severity Scale (FSS)</b>	Effect of <b>fatigue</b> on motivation, exercise, physical, social and family functioning	>5 fatigue



# Results: DTG PK

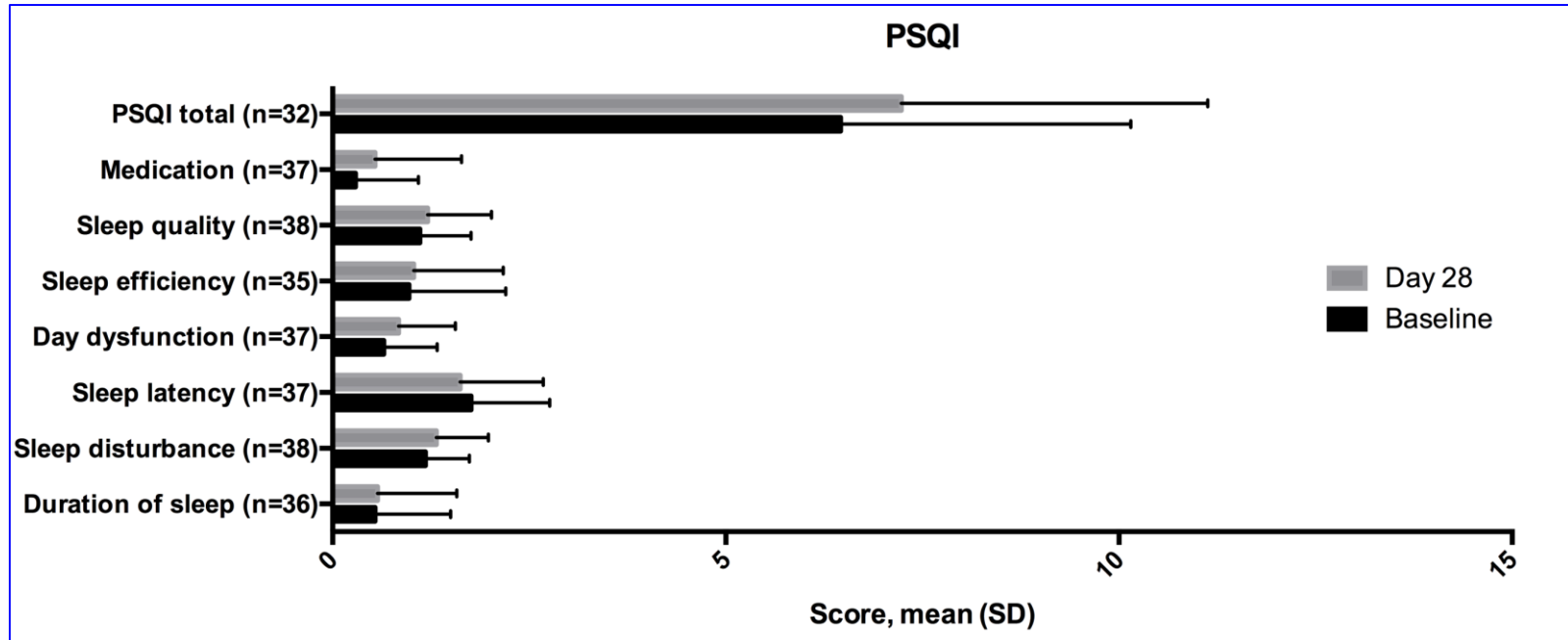


# Results: DTG PK

DTG **steady state PK parameters** in GMs with 95% CI and coefficient of variation, measured over **24hrs**:

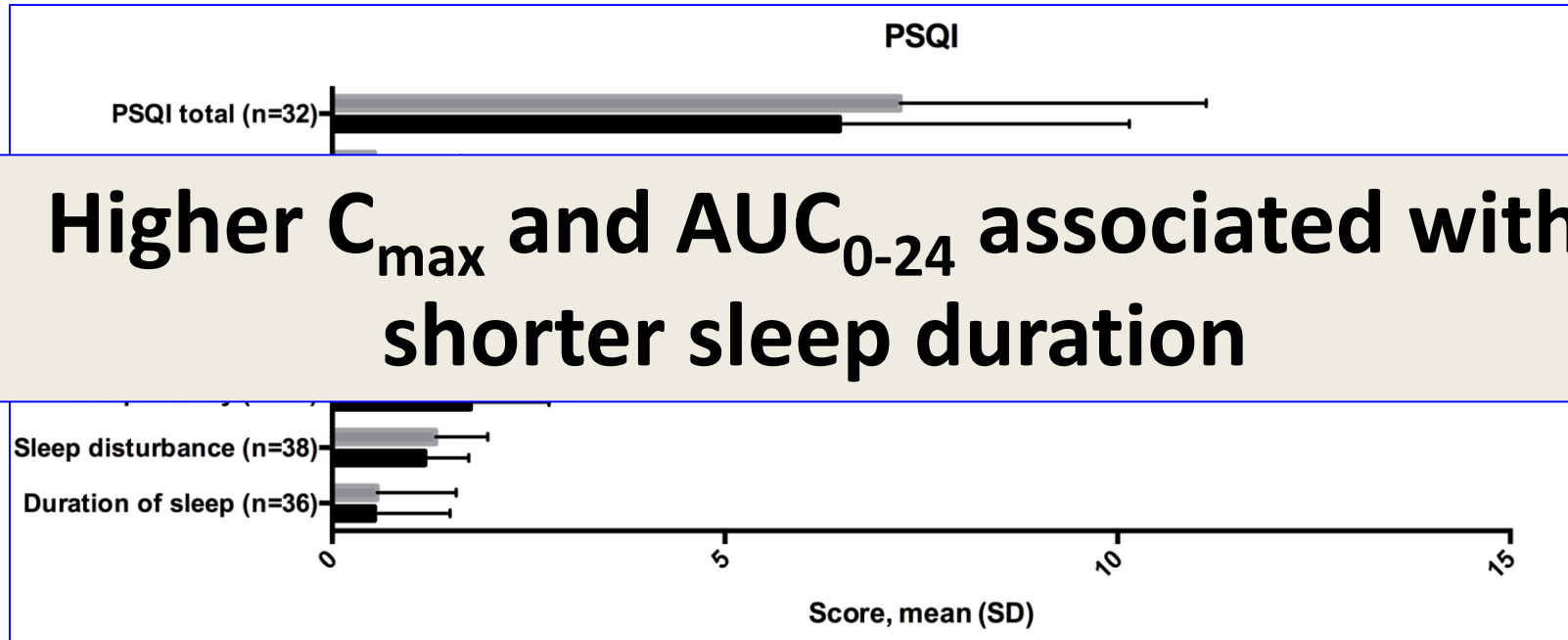
	Observed group (n=40)			Historical data (n=16)			P value (Mann-Whitney U)		
	$C_{max}$ (ng/ml)	$C_{min}$ (ng/ml)	AUC <sub>0-24</sub> (ng.h/ml)	$C_{max}$ (ng/ml)	$C_{min}$ (ng/ml)	AUC <sub>0-24</sub> (ng.h/ml)	$C_{max}$ (ng/ml)	$C_{min}$ (ng/ml)	AUC <sub>0-24</sub> (ng.h/ml)
Geomean	<b>4246</b>	1052	51799	<b>3402</b>	942	48068	<b>0.00496</b>	0.77182	0.56192
Low 95%	4018	999	49405	3008	799	42350	-	-	-
Up 95%	4767	1351	59020	4030	1461	59898	-	-	-
CV %	27	48	29	29	58	34	-	-	-

# Results: Pittsburgh Sleep Quality Index



**Sleep scores were not different at day 28 vs baseline (global and individual domains)**

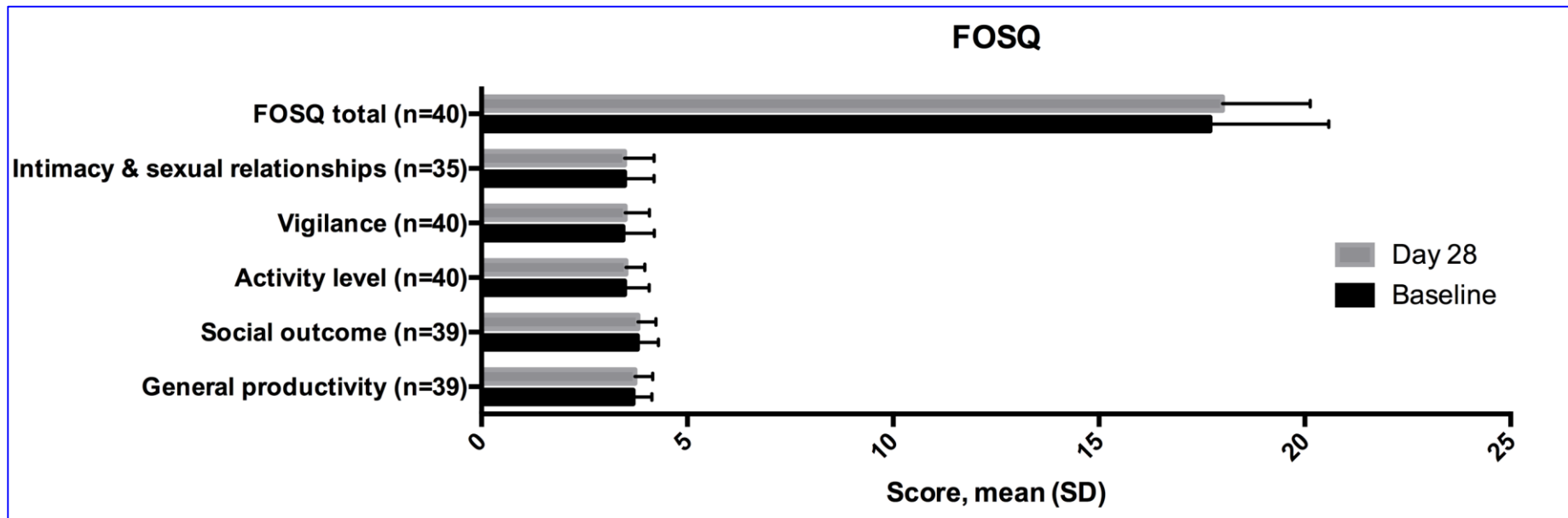
# Results: Pittsburgh Sleep Quality Index



**Higher  $C_{\max}$  and  $AUC_{0-24}$  associated with shorter sleep duration**

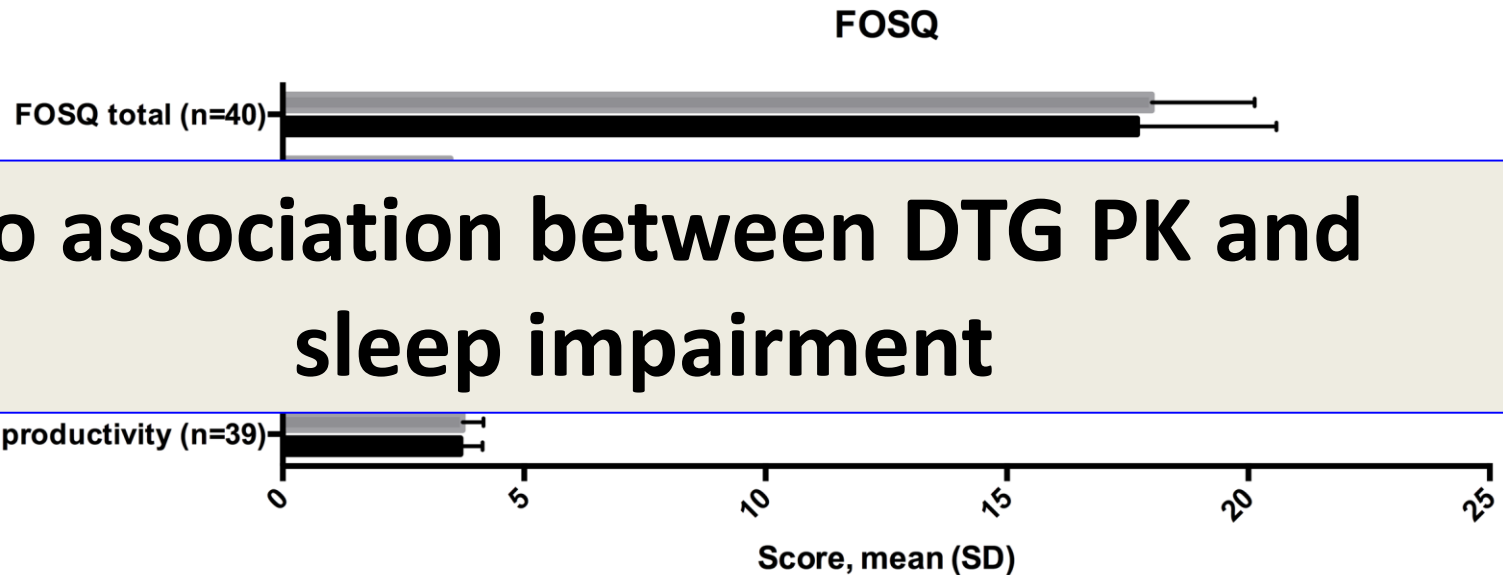
PSQI	Spearman correlation coefficient, p-value		
	$C_{\max}$	$C_{\min}$	$AUC_{0-24}$
Duration of sleep (n=36)	<b>0.330 (0.05)</b>	0.065 (0.71)	<b>0.353 (0.03)</b>
Sleep disturbance (n=38)	-0.100 (0.55)	0.077 (0.65)	-0.121 (0.47)
Sleep latency (n=37)	-0.247 (0.14)	0.038 (0.83)	-0.053 (0.75)
Day dysfunction (n=37)	-0.181 (0.28)	-0.200 (0.24)	-0.206 (0.22)
Sleep efficiency (n=35)	0.120 (0.49)	-0.136 (0.44)	0.032 (0.86)
Sleep quality (n=38)	-0.212 (0.20)	-0.153 (0.36)	0.207 (0.21)
Medication (n=37)	0.016 (0.92)	0.036 (0.83)	0.021 (0.90)
PSQI total (n=32)	0.074 (0.69)	-0.207 (0.26)	-0.042 (0.82)

# Results: Functional Outcomes of Sleep



**Sleep scores were not different at day 28 vs baseline (global and individual domains)**

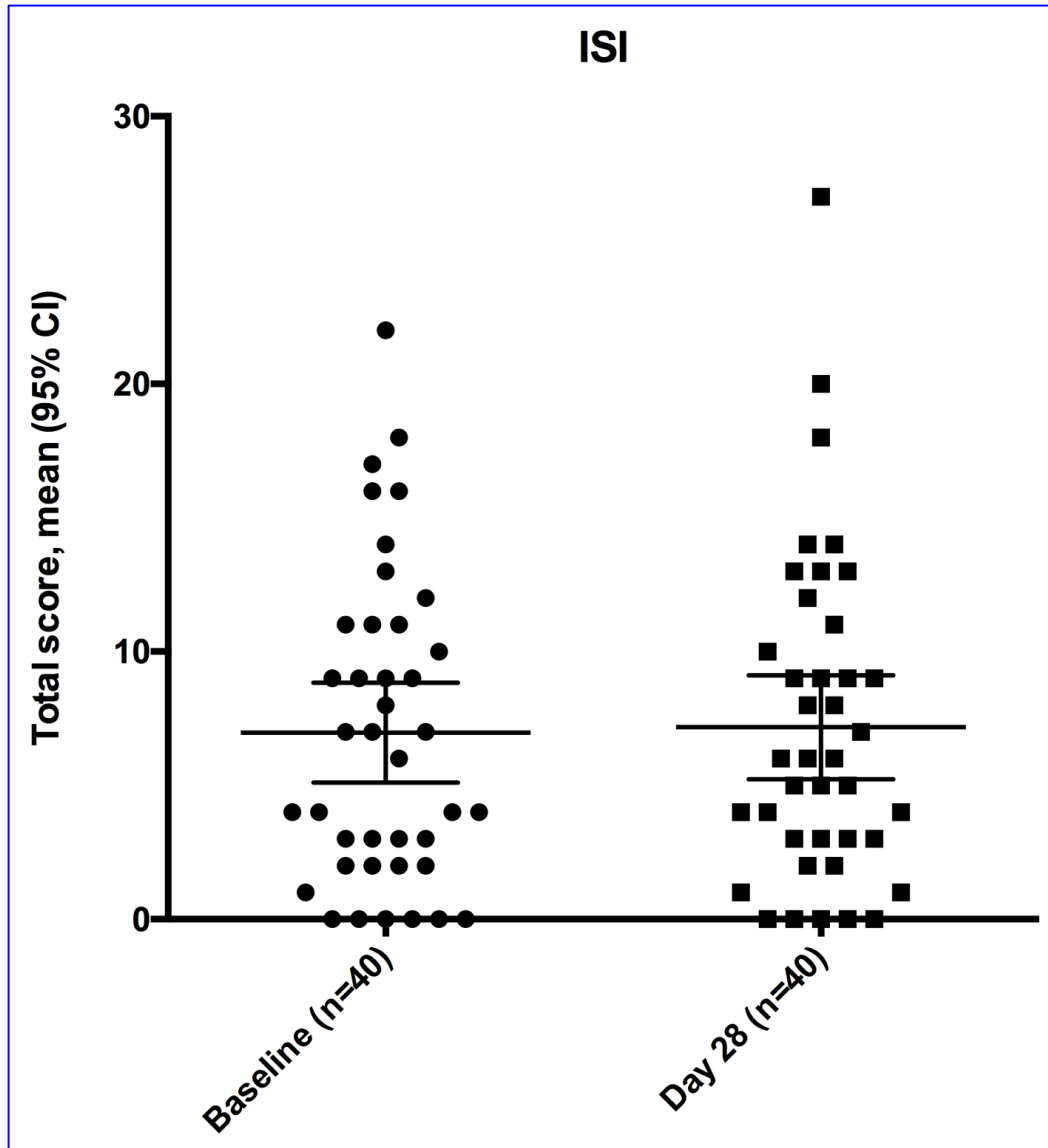
# Results: Functional Outcomes of Sleep



Spearman correlation coefficient, p-value

FOSQ	$C_{max}$	$C_{min}$	$AUC_{0-24}$
General productivity (n=39)	0.101 (0.54)	-0.068 (0.68)	-0.054 (0.75)
Social outcome (n=39)	-0.066 (0.69)	0.054 (0.74)	-0.039 (0.81)
Activity level (n=40)	0.065 (0.69)	0.008 (0.96)	0.005 (0.98)
Vigilance (n=40)	0.054 (0.74)	-0.237 (0.14)	-0.222 (0.17)
Intimacy & sexual relationships (n=35)	0.265 (0.12)	-0.284 (0.10)	0.043 (0.81)
FOSQ total (n=40)	0.108 (0.51)	-0.196 (0.23)	-0.117 (0.47)

# Results: Insomnia Severity Index



No change in scores between day 28 and baseline

No significant correlation observed between DTG PK parameters and ISI changes between day 28 and baseline

# Conclusions

In this study, in PLWH >60:

- Higher DTG  $C_{\max}$  compared to historical data ( $\neq$  absorption?)
- No significant changes in sleep scores at day 28 following a switch to ABC/3TC/DTG
- Higher DTG  $C_{\max}$  and AUC associated with shorter sleep duration (PSQI)
- ABC/3TC/DTG effective and well tolerated at day 28 of treatment, with no virological failures and no grade 3/4 toxicity



# Acknowledgements

- Study participants
- SSAT research team
- ViiV Healthcare for funding the study