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

DTG = dolutegravir; INSTI = xxx; PLWH = people living with HIV; CNS = central nervous system; AEs = adverse events; EFV = efavirenz

Van der Berck CROI 2016; Quercia HIVGlasgow 2016; Bracchi HIVGlasgow 2016
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

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

Day 90
- Adherence
- Concomitant meds
- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Viral Load
- DTG $C_{min}$

Day 180
- Adherence
- Concomitant meds
- Symptom-directed examination
- AEs
- Safety bloods
- Urinalysis
- Viral Load
- DTG $C_{min}$

Quality of life and Full Sleep Quality questionnaire set

Neurocognitive testing

Quality of life and Short Sleep Quality questionnaire set

Quality of life and Full Sleep Quality questionnaire set

Neurocognitive testing
Study design

**Day 1**
- Examination
- Concomitant meds
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Switch to ABC/3TC/DTG

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- AEs
- Safety bloods
- Urinalysis
- Viral load

**Intensive DTG PK sampling**

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- Adherence
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- Safety bloods
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- Viral load
- DTG $C_{min}$

**Quality of life and Full Sleep Quality questionnaire set**

**Neurocognitive testing**
## Materials & Methods

Protocol required enrolment of PLWH aged ≥60 years (30%) and ≥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

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

ADLs = activity of daily living
Results: DTG PK

C_{\text{max}} \text{ significantly higher} \text{ in patients aged } \geq 60 \text{ (p=0.005)}

Dolutegravir concentration (ng/mL)

Time (hours)

Over 60 (95% CI)
Controls under 50 (95% CI)

(DTG IC_{90}: 64ng/ml)

GM and 95%CI, n = 40
Results: DTG PK

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

<table>
<thead>
<tr>
<th></th>
<th>Observed group (n=40)</th>
<th>Historical data (n=16)</th>
<th>P value (Mann-Whitney U)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geomean</td>
<td>Historical data</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>4246</td>
<td>3402</td>
<td>0.00496</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>1052</td>
<td>942</td>
<td>0.77182</td>
</tr>
<tr>
<td>AUC$_0$-$24$ (ng.h/ml)</td>
<td>51799</td>
<td>48068</td>
<td>0.56192</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>4018</td>
<td>3008</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>999</td>
<td>799</td>
<td></td>
</tr>
<tr>
<td>AUC$_0$-$24$ (ng.h/ml)</td>
<td>49405</td>
<td>42350</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>-</td>
<td>4030</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/ml)</td>
<td>-</td>
<td>1461</td>
<td></td>
</tr>
<tr>
<td>AUC$_0$-$24$ (ng.h/ml)</td>
<td>-</td>
<td>59898</td>
<td></td>
</tr>
<tr>
<td>CV %</td>
<td>27</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>
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 $C_{\text{max}}$ and $\text{AUC}_{0-24}$ associated with shorter sleep duration

<table>
<thead>
<tr>
<th>PSQI</th>
<th>$C_{\text{max}}$</th>
<th>$C_{\text{min}}$</th>
<th>$\text{AUC}_{0-24}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sleep (n=36)</td>
<td>0.330 (0.05)</td>
<td>0.065 (0.71)</td>
<td>0.353 (0.03)</td>
</tr>
<tr>
<td>Sleep disturbance (n=38)</td>
<td>-0.100 (0.55)</td>
<td>0.077 (0.65)</td>
<td>-0.121 (0.47)</td>
</tr>
<tr>
<td>Sleep latency (n=37)</td>
<td>-0.247 (0.14)</td>
<td>0.038 (0.83)</td>
<td>-0.053 (0.75)</td>
</tr>
<tr>
<td>Day dysfunction (n=37)</td>
<td>-0.181 (0.28)</td>
<td>-0.200 (0.24)</td>
<td>-0.206 (0.22)</td>
</tr>
<tr>
<td>Sleep efficiency (n=35)</td>
<td>0.120 (0.49)</td>
<td>-0.136 (0.44)</td>
<td>0.032 (0.86)</td>
</tr>
<tr>
<td>Sleep quality (n=38)</td>
<td>-0.212 (0.20)</td>
<td>-0.153 (0.36)</td>
<td>0.207 (0.21)</td>
</tr>
<tr>
<td>Medication (n=37)</td>
<td>0.016 (0.92)</td>
<td>0.036 (0.83)</td>
<td>0.021 (0.90)</td>
</tr>
<tr>
<td>PSQI total (n=32)</td>
<td>0.074 (0.69)</td>
<td>-0.207 (0.26)</td>
<td>-0.042 (0.82)</td>
</tr>
</tbody>
</table>
Results: Functional Outcomes of Sleep

Sleep scores were not different at day 28 vs baseline (global and individual domains)
Results: Functional Outcomes of Sleep

No association between DTG PK and sleep impairment

<table>
<thead>
<tr>
<th>FOSQ</th>
<th>Spearman correlation coefficient, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$</td>
</tr>
<tr>
<td>General productivity (n=39)</td>
<td>0.101 (0.54)</td>
</tr>
<tr>
<td>Social outcome (n=39)</td>
<td>-0.066 (0.69)</td>
</tr>
<tr>
<td>Activity level (n=40)</td>
<td>0.065 (0.69)</td>
</tr>
<tr>
<td>Vigilance (n=40)</td>
<td>0.054 (0.74)</td>
</tr>
<tr>
<td>Intimacy &amp; sexual relationships (n=35)</td>
<td>0.265 (0.12)</td>
</tr>
<tr>
<td>FOSQ total (n=40)</td>
<td>0.108 (0.51)</td>
</tr>
</tbody>
</table>
Results: Insomnia Severity Index

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

No change in scores between day 28 and baseline
Conclusions

In this study, in PLWH >60:

• Higher DTG $C_{\text{max}}$ compared to historical data (≠ absorption?)

• No significant changes in sleep scores at day 28 following a switch to ABC/3TC/DTG

• Higher DTG $C_{\text{max}}$ 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