Dolutegravir (DTG), a second-generation HIV integrase inhibitor that is easily administered once daily, was shown to offer non-inferior efficacy in comparison with other medications in phase III trials. At present, DTG is increasingly being prescribed, particularly in developed countries, including Japan, and has been previously reported to induce side effects in the central nervous system (CNS), such as insomnia and headache. However, the mechanisms of action including associations between DTG plasma concentration and CNS side effects remain unclear.

The objective of this study was to examine the association between DTG plasma trough concentration and CNS side effects in Japanese HIV-1-infected patients. We recruited 162 HIV-infected patients who had undergone anti-retroviral treatment, including DTG, at Osaka National Hospital, Japan, between April 2014 and March 2016. DTG plasma trough concentration was measured, and the association between DTG concentration and CNS side effects was statistically analyzed within 6 months of DTG introduction. This study was performed at a single institution with a limited number of Japanese patients.

At least one CNS side effect was observed in 41 patients (25%), including dizziness (14/41, 34%), headache (11/41, 27%), insomnia (11/41, 27%), restlessness (4/41, 10%), and anxiety (3/41, 7%). Patients with CNS side effects showed higher trough DTG plasma concentrations compared with subjects without symptoms (median, 1.34 μg/ml vs 1.03 μg/ml, p=0.003 by univariate Mann-Whitney U-test). A positive correlation was observed between DTG concentration and frequency of CNS side effects (p=0.002 by Cochran-Armitage test).

No significant difference in DTG concentration was observed among CNS symptoms (p=0.56 by Kruskal-Wallis test).

This study was performed at a single institution with a limited number of Japanese patients.

We are grateful to all the study participants. This work was supported by the Research Program on HIV/AIDS from the Japan Agency for Medical Research and Development, AMED to K.Y.

In this study, a positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population. This implies the importance of measuring DTG concentration for evaluating CNS side effects.

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**Abstract #426**

**EFFECT OF DOLUTEGRAVIR PLASMA CONCENTRATION ON CENTRAL NERVOUS SYSTEM SIDE EFFECTS**

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**Background**

Dolutegravir (DTG), a second-generation HIV integrase inhibitor that is easily administered once daily, was shown to offer non-inferior efficacy in comparison with other medications in phase III trials. At present, DTG is increasingly being prescribed, particularly in developed countries, including Japan, and has been previously reported to induce side effects in the central nervous system (CNS), such as insomnia and headache. However, the mechanisms of action including associations between DTG plasma concentration and CNS side effects remain unclear.

**Patients & Methods**

We recruited 162 HIV-infected patients who had undergone anti-retroviral treatment, including DTG treatment, at Osaka National Hospital, Japan, between April 2014 and March 2016. DTG plasma trough concentration was measured, and the association between DTG concentration and CNS side effects was statistically analyzed within 6 months of DTG introduction. This study was performed at a single institution with a limited number of Japanese patients.

**Results**

We examined the association between DTG plasma trough concentration and CNS side effects (CNSSEs) in Japanese HIV-1-infected patients. Patients with CNS side effects showed higher trough DTG plasma concentrations compared with subjects without symptoms (median, 1.34 μg/ml vs 1.03 μg/ml, p=0.003 by univariate Mann-Whitney U-test). A positive correlation was observed between DTG concentration and frequency of CNS side effects (p=0.002 by Cochran-Armitage test).

No significant difference in DTG concentration was observed among CNS symptoms (p=0.56 by Kruskal-Wallis test).

**Conclusions**

In this study, a positive correlation between DTG plasma trough concentration and CNS side effects was identified in a Japanese population. This implies the importance of measuring DTG concentration for evaluating CNS side effects.

**Limitations**

This study was performed at a single institution with a limited number of Japanese patients.

**Acknowledgments**

We are grateful to all the study participants. This work was supported by the Research Program on HIV/AIDS from the Japan Agency for Medical Research and Development, AMED to K.Y.

**References**


**Table 1. Demographics of participants**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Without CNSSEs</th>
<th>With CNSSEs</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (n, %)</td>
<td>162</td>
<td>121 (75%)</td>
<td>41 (25%)</td>
<td></td>
</tr>
<tr>
<td>Age (years), median [IQR]</td>
<td>43 [38–52]</td>
<td>43 [38–52]</td>
<td>42 [36–48]</td>
<td>0.1754</td>
</tr>
<tr>
<td>Males (n, %)</td>
<td>154(95%)</td>
<td>115 (95%)</td>
<td>39 (95%)</td>
<td>0.6918</td>
</tr>
<tr>
<td>Treatment-naïve (n, %)</td>
<td>36 (22%)</td>
<td>23 (19%)</td>
<td>13 (32%)</td>
<td>0.1407</td>
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<tr>
<td>Taking at bedtime (n, %)</td>
<td>12 (7%)</td>
<td>10 (8%)</td>
<td>2 (5%)</td>
<td>0.9778</td>
</tr>
<tr>
<td>Participants with HIV-1-RNA level &lt;50 at time of sampling (n, %)</td>
<td>158 (98%)</td>
<td>115 (95%)</td>
<td>39 (95%)</td>
<td>0.6918</td>
</tr>
<tr>
<td>Use of antiretroviral agents (n, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenovir</td>
<td>80 (49%)</td>
<td>55 (45%)</td>
<td>25 (61%)</td>
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</tr>
<tr>
<td>Abacavir</td>
<td>72 (45%)</td>
<td>59 (49%)</td>
<td>13 (32%)</td>
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<tr>
<td>Protease inhibitor</td>
<td>5 (3%)</td>
<td>4 (3%)</td>
<td>1 (2%)</td>
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<td>NNRTI</td>
<td>92 (57%)</td>
<td>67 (55%)</td>
<td>25 (61%)</td>
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<td>HIVB infection (n, %)</td>
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<tr>
<td>HCV infection (n, %)</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td>0.9919</td>
</tr>
</tbody>
</table>

**Figure 1. Comparison of DTG plasma-trough concentration between patients with and without CNSSEs. Horizontal straight line indicates median value.**

**Figure 2. Association between DTG plasma-trough concentration and CNSSEs rate.**

**Figure 3. Comparison of DTG plasma-trough concentrations according to symptoms of CNSSEs.**