Crushing of dolutegravir combination tablets increases dolutegravir exposure

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Introduction
If HIV-patients are unconscious or cannot swallow tablets for other reasons, antiretroviral medication is often crushed and dissolved prior to administration. Crushing can influence pharmacokinetics (PK) leading to altered drug exposure, possibly leading to treatment failure, development of resistance or toxicity.

Currently there is no information about crushing the brand fixed-dose combination of dolutegravir (DTG) / abacavir (ABC) / lamivudine (3TC) (Triumeq®, TRI), therefore crushing TRI is not recommended.

PK interaction between DTG and enteral nutrition is possible, based on the known interaction between DTG and cations in antacids and dietary supplements.

Objective
To investigate whether the branded fixed-dose combination tablet of dolutegravir/abacavir/lamivudine can be crushed and combined with enteral nutrition without influencing pharmacokinetics.

Material & Methods

- The Subjects were 22 male volunteers (21 Caucasian and 1 mixed-race, 10 female), 25 (18-54) years old and BMI 23 (20-27) kg/m² (median) were included.
- Intervention I: reference treatment; a crushed tablet was not bio-equivalent to the whole tablet, since DTG AUC_{0-24h} and C_{max} increased with 26% and 30% respectively (see Table 2) and the corresponding 90% CIs of GMRs fell outside the predefined bio-equivalence range of 80-125%.
- Intervention II: crushed tablet combined with enteral nutrition; treatment with enteral nutrition to a whole tablet TRI, fell outside the predefined bio-equivalence range and therefore bio-equivalence could not be demonstrated.
- DTG, ABC and 3TC plasma concentrations were analysed by use of validated LC-MS/MS methods.
- PK parameters were determined using a non-compartmental analysis in Phoenix/WinNonlin version 6.3.

Results
- 22 healthy volunteers (21 Caucasian and 1 mixed-race, 10 female), 25 (18-54) years old and BMI 23 (20-27) kg/m² (median) were included.
- Intervention I vs. reference treatment; a crushed tablet is not bio-equivalent to the whole tablet, since DTG AUC_{0-24h} and C_{max} increased with 26% and 30% respectively (see Figure 2) and the corresponding 90% CIs of GMRs fell outside the predefined bio-equivalence range of 80-125% (Table 1). For ABC and 3TC the GMRs and 90% CI for AUC_{0-24h} and C_{max} fell within 80-125%.
- Intervention II vs. reference treatment; for the crushed tablet with enteral nutrition DTG C_{max} increased with ca. 21% compared to the whole tablet fasted. ABC C_{max} decreased with 17% (see table 1).
- The 90% CIs of GMRs for C_{max} of both DTG and ABC compared with a crushed TRI tablet with enteral nutrition to a whole tablet TRI, fell outside the predefined bio-equivalence range and therefore bio-equivalence could not be demonstrated (see Table 1).

Discussion & Conclusion
- DTG exposure was higher after crushing and after crushing followed by drinking enteral nutrition compared to the whole tablet, all in fasted conditions. The maximum concentrations showed the same trend. The half-life was similar in all treatments, therefore increased DTG exposure is probably caused by enhanced absorption. Enteral nutrition did not have a relevant negative impact on absorption.
- The increased DTG exposure is considered not clinically relevant, since DTG exposure if taken in with food or in BID dosing exceeds our results [12]. The decreased ABC C_{max} (intervention II) is in line with other studies for ABC taken with food and considered not clinically relevant [12].
- The combination of BID dosing, intake with food and crushing TRI though can lead to even higher plasma concentrations, while there is no information on dose-limiting toxicity for DTG in clinical practice to date.
- Our results are comparable to the results for crushed eltegravir combination tablets (Stiribid®) compared to the whole tablet and intake with breakfast [10].

Conclusion
In our opinion TRI can be crushed for patients with swallowing difficulties or with an enteral feeding tube and can be combined with enteral nutrition without separating intake in time. Although no dose-limiting toxicity of DTG is observed to date, crushing dolutegravir is advised against if BID dosing and intake with food is needed.

Acknowledgements
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References

Table 1: PK parameters for dolutegravir, abacavir and lamivudine and GMRs.

<table>
<thead>
<tr>
<th>PK-parameter</th>
<th>Reference treatment (whole tablet, fasting)</th>
<th>Intervention I (crushed tablet, fasting)</th>
<th>Intervention II (crushed tablet combined with enteral nutrition)</th>
<th>Intervention I vs. reference treatment GMR (90% CI)</th>
<th>Intervention II vs. reference treatment GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG AUC_{0-24h} (ng·h/L)</td>
<td>90.50 (22)</td>
<td>87.49 (23)</td>
<td>82.38 (25)</td>
<td>125.8 (119-133)</td>
<td>118.4 (112-125)</td>
</tr>
<tr>
<td>C_{max} (ng/L)</td>
<td>3.85 (24)</td>
<td>4.94 (28)</td>
<td>4.66 (31)</td>
<td>129.5 (123-136)</td>
<td>121.7 (115-128)</td>
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<tr>
<td>T_{max} (h)</td>
<td>2.27 (1.00-4.02)</td>
<td>2.00 (1.00-3.00)</td>
<td>2.50 (1.00-4.02)</td>
<td>125.8 (119-133)</td>
<td>118.4 (112-125)</td>
</tr>
<tr>
<td>ABC AUC_{0-24h} (ng·h/L)</td>
<td>14.40 (29)</td>
<td>14.31 (29)</td>
<td>15.31 (28)</td>
<td>99.4 (95-104)</td>
<td>94.1 (90-98)</td>
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<td>C_{max} (ng/L)</td>
<td>4.86 (36)</td>
<td>4.95 (31)</td>
<td>4.60 (22)</td>
<td>101.0 (93-109)</td>
<td>83.0 (76-89)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>1.00 (0.50-3.00)</td>
<td>1.00 (0.50-2.00)</td>
<td>1.58 (0.50-3.00)</td>
<td>101.0 (93-109)</td>
<td>83.0 (76-89)</td>
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<tr>
<td>3TC AUC_{0-24h} (ng·h/L)</td>
<td>3.87 (21)</td>
<td>4.33 (24)</td>
<td>4.55 (22)</td>
<td>101.0 (93-109)</td>
<td>100.6 (96-105)</td>
</tr>
<tr>
<td>C_{max} (ng/L)</td>
<td>2.53 (31)</td>
<td>2.28 (23)</td>
<td>2.47 (11)</td>
<td>98.6 (93-105)</td>
<td>106.7 (100-113)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>2.00 (1.00-3.00)</td>
<td>1.90 (1.00-4.00)</td>
<td>2.00 (1.00-5.00)</td>
<td>101.0 (93-109)</td>
<td>83.0 (76-89)</td>
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<tr>
<td>T (h)</td>
<td>12.60 (19)</td>
<td>12.66 (32)</td>
<td>12.67 (27)</td>
<td>101.0 (93-109)</td>
<td>83.0 (76-89)</td>
</tr>
</tbody>
</table>

Presented data are geometric means (90% CI) or geometric mean ratios, GMR (90% CI). Values for T_{max} are presented as median (range). T_{max} is the apparent elimination half-life. DTG=dolutegravir; ABC=abacavir; 3TC=lamivudine.